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Original Article



Scoring system for identifying Japanese patients with COVID-19 at risk of requiring oxygen supply: A retrospective single-center study

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ABSTRACT

Introduction: Japan is facing the threat of medical system collapse due to the rapid spread of coronavirus disease 2019 (COVID-19). The present scoring system may help assess disease severity and oxygen supply requirements in COVID-19 patients.

Methods: Data on patient characteristics at baseline and throughout hospitalization for COVID-19 were extracted from medical records. Disease severity was dichotomized into two categories without or with oxygen supply as asymptomatic, mild, and moderate illness (AMMI), and severe and critical illness (CSI). The AMMI and CSI groups were compared. Predictors of disease severity, previously identified in the outpatient setting, were included in multivariable logistic regression analysis; the obtained coefficients were converted to integers and assigned a score.

Results: A total of 206 patients diagnosed with COVID-19 were included in this study. Correlation between COVID-19 severity and medical information was examined by comparing AMMI and CSI. Age, hemodialysis, and C-reactive protein (CRP) levels were candidate predictors of the need for oxygen supply in patients with COVID-19. Coefficients associated with age, hemodialysis, and CRP were as follows: $1 \times \text{age}$ (in years, coded as 0 for values of <50 , and as 1 for values of ≥ 50) + $1 \times \text{hemodialysis}$ (coded as 0 for “no”, and as 1 for “yes”) + $1 \times \text{CRP}$ (in mg/dL, coded as 0 for values of <1.0 , and as 1 for values of ≥ 1.0). Patients with scores of ≥ 2 points required oxygen supply (sensitivity, 68.4%; specificity, 79.0%).

Conclusion: The present model can help predict disease severity and oxygen requirements in COVID-19 patients in Japan.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, Hubei Province, China, and has spread worldwide shortly thereafter [1]. On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. Globally, as of January 17, 2021, there have been 92, 506, 811 and 2,001,773 confirmed cases and

associated deaths, respectively, reported worldwide [2]. The corresponding values for Japan, as of January 17, 2021, are 315,910 and 4,380, respectively [2]. Despite global efforts to contain the pandemic, several countries including Japan, are facing the threat of medical system collapse [3–5].

Most COVID-19 patients are concurrently asymptomatic and infectious [6]. However, COVID-19 is associated with high morbidity and mortality rates among symptomatic patients. Most patients that rapidly develop acute respiratory distress syndrome require mechanical

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Abbreviation

COVID-19	Coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
BMI	body mass index
HT	hypertension
DM	diabetes mellitus
CVD	cardiovascular diseases
HIV	human immunodeficiency virus
NLR	neutrophil-to-lymphocyte ratio
AST	aspartate aminotransferase
ALT	alanine aminotransferase
LDH	lactate dehydrogenase
BUN	blood urea nitrogen
CRP	C-reactive protein
RBS	random blood sugar
KL-6	Krebs von den Lungen-6
CT	computed tomography
OECD	Organization for Economic Co-operation and Development

ventilation; a high proportion of patients with the severe disease die as a result of it [7,8]. To prevent medical system collapse, patients likely to develop severe or critical illness should be identified and hospitalized. Previous studies have proposed prediction models focused on COVID-19 diagnosis and prognosis in the general population [9]; however, no model has been proposed to date for predicting disease severity and the need for oxygen supply, which correspond to the need for hospitalization.

In Japan, the number of acute beds per 1000 people is larger than that in other countries that are members of the Organization for Economic Co-operation and Development (OECD) [10]. However, the number of physicians per 1000 people ranks Japan in the middle among the OECD member countries [11]. In addition, in Japan, COVID-19 has been designated as a Category II infectious disease under the Infectious Diseases Control Law; this means that infected patients are required to either be hospitalized or isolated at home or specialized hotels. Given these requirements, effective screening of high-risk patients is required in Japan to prevent medical system collapse.

This retrospective study aimed to develop a scoring system that helps effectively and efficiently identify patients at risk of severe COVID-19 in the outpatient setting, including those likely to require oxygen supply, as relevant in the Japanese context.

2. Materials and methods

The study protocol was approved by the Institutional Review Board of the Osaka Habikino Medical Center (approval no. 1057). This study was conducted according to the tenets of the 1964 Declaration of Helsinki and its later amendments. This study was performed based on the institutional opt-out policy (<http://www.ra.opho.jp/hospital/110/>), which is an alternative to acquiring informed consent from patients.

2.1. Patient selection and setting

Consecutive adult Japanese (≥ 18 years) patients diagnosed with SARS-CoV-2 viral infection were included in this study. Patients of foreign origin or aged < 18 years were excluded from this study. Patients who were already on oxygen support at the time of admission were excluded from this study. Therefore, in this study, we selected the patients who were admitted without oxygen inhalation to the Osaka Habikino Medical Center between February 20 and November 16, 2020.

2.2. Detection of SARS-CoV-2

The genetic detection of SARS-CoV-2 was performed using polymerase chain reaction or loop-mediated isothermal amplification at our institution or the Osaka Institute of Public Health.

2.3. Data collection

We extracted data on the following variables from the patients' medical records: demographic characteristics (age, sex, height, body weight, smoking history), comorbidities (hypertension [HT], diabetes mellitus [DM], cardiovascular diseases [CVD], chronic lung diseases, kidney diseases, cerebrovascular diseases, cancer, hyperuricemia, dyslipidemia, depression, dementia, and human immunodeficiency virus [HIV]). Furthermore, we extracted information on laboratory findings obtained on the day of or before hospitalization, specifically: white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet count, serum albumin levels, aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, lactate dehydrogenase (LDH) levels, blood urea nitrogen (BUN) levels, creatinine levels, C-reactive protein (CRP) levels, ferritin levels, D-dimer levels, Krebs von den Lungen-6 (KL-6) protein levels, and random blood sugar (RBS) levels.

2.4. COVID-19 severity and assessment timing

COVID-19 severity was defined according to the National Institutes of Health COVID-19 treatment guidelines [12]. Patients with asymptomatic, mild, or moderate illness (AMMI) were those that did not require oxygen supply at all during hospitalization. In contrast, patients categorized as having a severe or critical illness (CSI) were those that required oxygen supply during hospitalization. Disease severity was evaluated throughout hospitalization and peak severity was used to define patient severity status in this study.

2.5. Treatment

Antiviral and anti-inflammatory treatments were administered to most patients, following our institution's COVID-19 treatment guidelines (Table 1).

2.6. Study outcomes

Risk factors and stratification scores for oxygen supply need among Japanese patients with COVID-19 were evaluated based on clinical characteristics, and laboratory on admission day. Since hospitalization is mandatory when oxygen supply is required, the need for oxygen was the primary outcome and indicator of disease severity.

2.7. Statical analysis

Continuous variables were presented as medians with interquartile ranges. Categorical variables were presented as counts and percentages. Between-group comparisons of continuous variables were performed using the Mann-Whitney *U* test, whereas categorical variables were compared using the Fisher exact test. No imputation was performed for missing data. Between-group differences were considered statistically significant at *p*-values of < 0.05 .

The following protocol was implemented to build a risk score. Univariate logistic regression analysis was performed to assess the effect of independent variables on the risk of severe disease. Subsequently, predictors with *p*-values of < 0.05 in univariate analysis, and those that can be effectively and efficiently used in the outpatient setting were included in multivariable logistic regression analysis. Odds ratios and 95% confidence intervals, and their corresponding *p*-values were calculated; findings were considered statistically significant at *p*-values

Table 1
Summary of the COVID-19 treatment guidelines of the Osaka Habikino Medical Center.

Severity	Antiviral treatments		Anti-inflammatory treatments		
Asymptomatic and mild illness	Ivermectin	(Ciclesonide)			
Moderate illness	(Ciclesonide)	Favipiravir			
Severe illness	Favipiravir	(Lopinavir/ritonavir)	Dexamethasone		
Critical illness	Favipiravir	(Lopinavir/ritonavir)	Dexamethasone	Tocilizumab	high-dose methylprednisolone pulse therapy

These guidelines have been updated five times since launch. Treatments presented in parentheses represent drugs no longer used.

of <0.05. Finally, risk scores were assigned based on the value of logistic regression coefficients. The total score represented the clinical risk score and was divided into two categories: low-risk and high-risk.

For logistic regression analyses, continuous variables were converted to categorical variables, based on the upper or lower limit of the normal range, median values, or receiver operating characteristic (ROC) curve analysis findings (Fig. 1), as follows: age (≥ 50 years), BMI (≥ 22.0 kg/m²), white blood cell count (≥ 8601 /L), neutrocyte count ($\geq 2,885 \times 10^6$ /L), lymphocyte count ($\geq 1,143 \times 10^6$ /L), neutrophil and lymphocyte count (≥ 4.0), platelet count ($\geq 350,000$ /L), aspartate aminotransferase levels (≥ 31 U/L), alanine aminotransferase levels (≥ 43 U/L), LDH levels (≥ 223 IU/L), BUN levels (≥ 20.1 mg/dL), creatinine levels (≥ 1.08 mg/dL), CRP levels (≥ 1 mg/dL), ferritin levels (≥ 303.8 ng/mL), D-dimer levels (≥ 1.0 ng/mL), KL-6 levels (≥ 500 U/mL), and RBS levels (≥ 110 mg/dL). All statistical analyses were performed in R software, version 3.6.3 (R version 3.6.3, <https://www.r-project.org/>, accessed June 20, 2020).

3. Results

A total of 206 patients diagnosed with COVID-19 were included in this study (Table 2). Among them, 38 (18.4%) and 168 (81.6%) patients were classified as CSI and AMMI, respectively. The patients' median age was 49.5 years. CSI patients were significantly older than AMMI patients (74 [53.3–79.8] vs 44.5 [25.8–71], $p < 0.001$). CSI patients had a higher body mass index (BMI) than did AMMI patients (24.4 [21.1–26.7] vs. 21.6 [20.0–24.9], $p = 0.016$). Moreover, patients with CSI were more likely of having HT and DM and undergoing hemodialysis than were those with AMMI ($p < 0.001$, <0.001 and 0.008 respectively). No significant between-group difference was observed in the prevalence of chronic lung disease, CVD, cancer, hyperuricemia, hyperlipidemia, or HIV.

4. COVID-19 severity and laboratory at hospitalization

NLR ($p < 0.001$), and the levels of LDH ($p < 0.001$), BUN ($p = 0.002$), creatinine ($p < 0.001$), CRP ($p < 0.001$), ferritin ($p = 0.001$), D-dimer ($p = 0.03$), KL-6 ($p = 0.007$), and RBS ($p < 0.001$) were higher in CSI patients than in AMMI patients.

Lymphocyte count ($p < 0.001$), platelet count ($p < 0.001$), and serum albumin levels ($p = 0.001$) were significantly lower in CSI than in AMMI patients (Table 3).

4.1. Predictors of need for oxygen supply and development of clinical risk score

Of 8 predictors identified in univariate analysis, we selected age, BMI, hemodialysis status, NLR, serum albumin, and CRP levels as potential predictors of the need for hospitalization in patients with COVID-19. Due to a large number of patients with missing data (63/206), the levels of ferritin were excluded as variables. As the values of NLR and lymphocyte count were overlapped, lymphocyte count was excluded from further analysis.

Test coefficients associated with age, hemodialysis status, and the levels of CRP were derived from logistic regression analysis and converted into integers; subsequently, they were assigned a score of 1, 1,

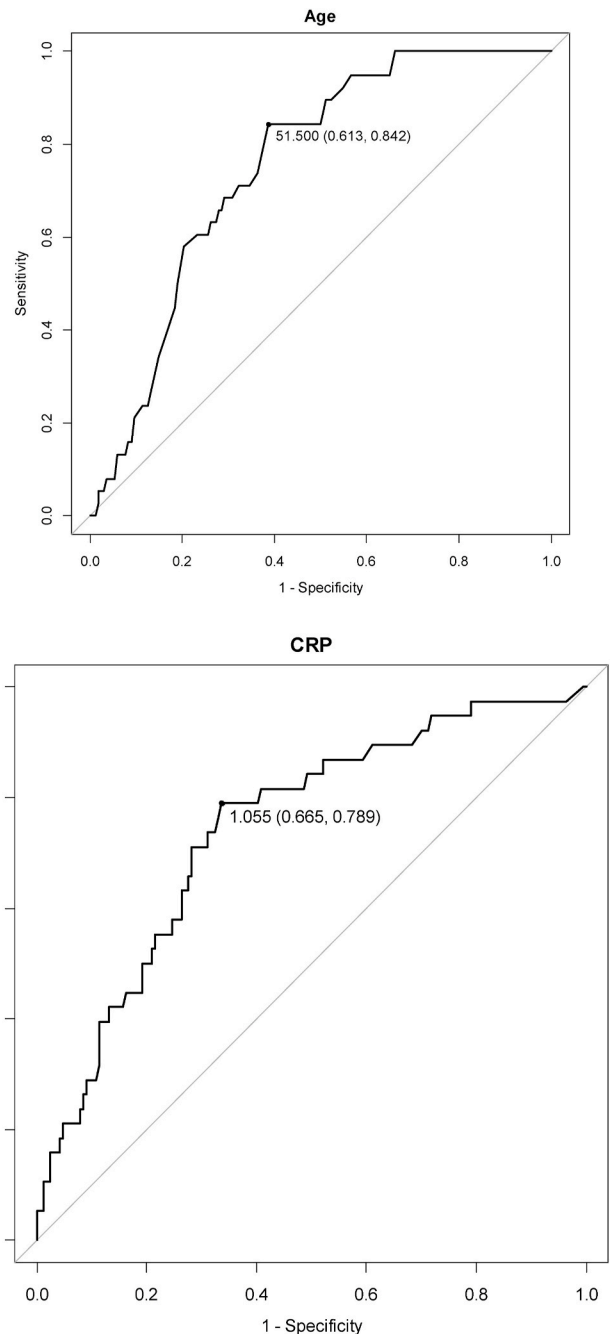


Fig. 1. Receiver operating characteristic curves for age (A) and C-reactive protein (CRP [B]) in COVID-19 severity assessment.

and 1, respectively, yielding the risk score formula of $1 \times \text{age}$ (in years, coded as 0 for values of <50 , and as 1 for values of ≥ 50) + $1 \times \text{hemo-dialysis}$ (coded as 0 for “no”, and as 1 for “yes”) + $1 \times \text{CRP}$ (in mg/dL, coded as 0 for values of <1.0 , and as 1 for values of ≥ 1.0) (Table 4).

Table 2
Patients' demographic and clinical characteristics on admission.

	Count (%) or median (IQR)	COVID-19 severity		p-value
		CSI	AMMI	
Number of patients	206	38	168	
Patient characteristics				
Age (years)	49.5 (29.5–73)	74 (53.3–79.8)	44.5 (25.8–71)	<0.001
Sex at birth				
Female	88 (42.7%)	14 (36.8%)	74 (44.0%)	0.42
Smoking status				
Ever	84 (40.8%)	16 (42.1%)	68 (40.5%)	0.8
Mean time from onset to hospital (days)	4 (2–7)	3 (2–7)	4 (2–6.5)	0.64
Mean body mass index (kg/m ²)	22.0 (20.1–25.4)	24.4 (21.1–26.7)	21.6 (20.0–24.9)	0.016
Comorbidity: Yes				
Hypertension	59 (28.6%)	20 (52.6%)	39 (23.2%)	<0.001
Diabetes	21 (10.2%)	10 (26.3%)	11 (6.6%)	<0.001
Chronic lung disease	33 (16.0%)	6 (15.8%)	27 (16.1%)	0.966
Cardiovascular disease	27 (13.1%)	7 (18.4%)	20 (11.9%)	0.282
Hemodialysis	10 (4.9%)	5 (13.2%)	5 (3.0%)	0.008
Cancer	4 (1.9%)	1 (2.6%)	3 (1.8%)	0.561
Hyperuricemia	12 (5.8%)	4 (10.5%)	8 (4.8%)	0.24
Hyperlipidemia	16 (7.8%)	4 (10.5%)	12 (7.1%)	0.503
Human Immunodeficiency Virus	8 (3.9%)	1 (2.6%)	7 (4.2%)	1

CSI: critical/severe illness, AMMI: asymptomatic/mild/moderate illness.

The area under the curve for this clinical risk score was 0.809; the risk score ranged from 0 to 3 points. Patients with scores of ≥ 2 points required oxygen supply and hospitalization (sensitivity, 68.4%; specificity, 79.0%) (Table 5 and Fig. 2).

5. Discussion

This study aimed to develop a scoring system for efficient and effective prediction of COVID-19 severity and the need for oxygen supply among Japanese patients. To this end, we examined factors associated with the need for oxygen supply during hospitalization. The

Table 3
Laboratory findings on admission.

	Count (%) or median (IQR)	COVID-19 severity		p-value
		CSI	AMMI	
Number of patients	206	38	168	
Laboratory findings				
White blood cell (x 10 ³ /L)	4.6 (3.9–5.9)	4.6 (3.9–5.7)	4.7 (3.8–5.9)	0.947
Neutrocyte count (x 10 ⁶ /L)	2885 (2248–4068)	3130 (2755–4228)	2840 (2153–4010)	0.056
Lymphocyte count (x 10 ⁶ /L)	1143 (910–1563)	870 (660–1125)	1265 (983–1610)	<0.001
Neutrophil-to-lymphocyte ratio	2.5 (1.7–3.9)	3.9 (2.6–5.6)	2.3 (1.6–3.4)	<0.001
Platelet count (x 10 ⁶ /L)	18.8 (15.6–22.9)	15.5 (12.1–17.6)	19.3 (16.4–24.5)	<0.001
Serum albumin (g/dL)	4.1 (3.6–4.4)	3.7 (3.4–4.1)	4.1 (3.6–4.4)	0.001
Aspartate aminotransferase (IU/L)	24 (18–32)	28 (20–34)	23 (17–31)	0.079
Alanine aminotransferase (IU/L)	19 (13–30)	20 (12–27)	19 (13–31)	0.588
Lactate dehydrogenase (IU/L)	191 (158–235)	223 (196–267)	184 (153–227)	<0.001
Blood urea nitrogen (mg/dL)	13.3 (10.2–17.0)	15.7 (13.6–18.3)	12.4 (9.8–16.6)	0.002
Creatinine (mg/dL)	0.8 (0.65–0.97)	0.96 (0.77–1.21)	0.78 (0.62–0.92)	<0.001
C-reactive protein (mg/dL)	0.8 (0.2–2.78)	2.71 (1.11–5.89)	0.54 (0.17–2.17)	<0.001
Ferritin (ng/mL)	182.8 (83.8–341.3)	319 (170.3–665.6)	148.5 (66.1–290.0)	0.001
D-dimer (ng/mL)	0.5 (0.5–1.3)	0.8 (0.5–1.5)	0.5 (0.5–0.9)	0.03
KL-6 (U/mL)	204 (163–290)	297 (183–363)	196 (160–261)	0.007
Blood sugar (mg/dL)	103 (93–117)	116 (103–139)	101 (92–112)	<0.001

CSI: critical/severe illness, AMMI: asymptomatic/mild/moderate illness.

KL-6: Krebs von den Lungen-6.

proposed scoring system may help select patients at high risk of requiring oxygen supply, helping to prioritize admissions and to prevent medical system collapse, as the number of COVID-19 patients continues to increase. The present model predicts COVID-19 severity based on simple indicators that are easy to obtain such as patient age, hemodialysis status, and the levels of CRP.

The total clinical risk score ranged from 0 to 3 points; patients were

Table 4
Multiple logistic regression analysis and Point allocation for predictors.

	OR	95.0% CI	p-value
Age (reference: <50 years)			
≥ 50 years	9.26	2.9–29.57	<0.001
BMI (reference: <22 kg/m²)			
≥ 22 kg/m ²	1.76	0.71–4.33	0.218
Hemodialysis			
Yes	5.51	1.08–28.1	0.041
Neutrophil-to-lymphocyte ratio (reference: <4.0)			
≥ 4.0	2.22	0.89–5.53	0.088
Serum albumin (reference: >4.1 g/dL)			
≤ 4.1 g/dL	2.8	0.9–8.72	0.068
C-reactive protein (reference: <1.0 mg/dL)			
Yes	6.49	2.14–19.69	<0.001
Point allocation for predictors			
	Beta coefficient		Score assigned
Age			
≥ 50 years	2.225		1
Hemodialysis			
Yes	1.706		1
C-reactive protein			
≥ 1.0 mg/dL	1.87		1

Table 5
Clinical risk score and the corresponding number of patients.

Score	Number of patients	
	CSI	AMMI
0	0	69
1	12	63
2	23	34
3	3	1

CSI: critical/severe illness, AMMI: asymptomatic/mild/moderate illness.

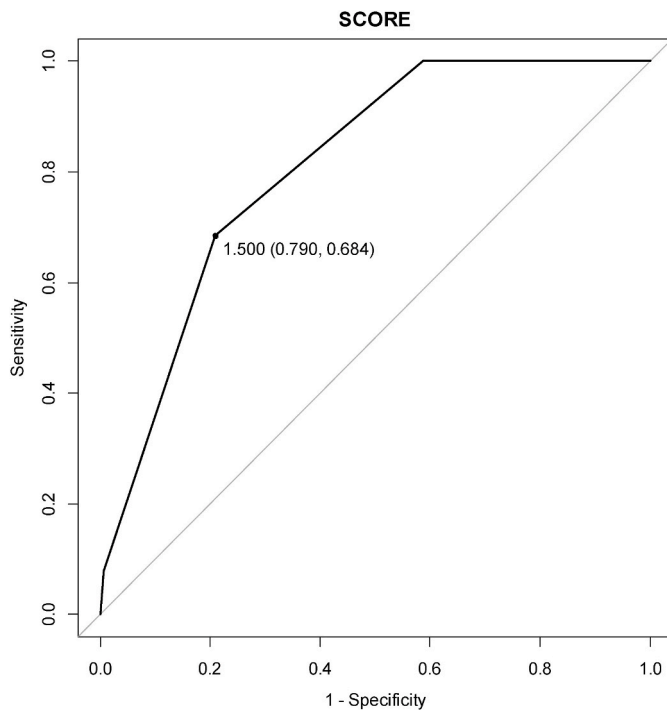


Fig. 2. Receiver operating characteristic curve for the clinical risk score. The area under the curve for oxygen supply is 0.809.

dichotomized based on their need for oxygen supply and divided into two groups based on the cut-off score of 2 points (sensitivity, 68.4%; specificity, 79.0%). The evidence presented in Table 5 suggests that this score may be used to divide patients into three categories, based on their need for hospitalization, with scores of 0, 1, and 2–3 points corresponding to extremely low (no need for oxygen [0/69]), low (16.0% of patients need oxygen [12/75]), and high risk (42.6% of patients need oxygen [26/61]), respectively. These categories may represent the risk of a patient progressing to severe or critical disease. Patients at extremely low risk would remain in isolation and under surveillance, while those at low risk (1 point) would require general admission at hospitals. Furthermore, patients with high risk (2–3 points) would require admission for specialist COVID-19 care.

The use of this patient stratification model may help prevent medical system collapse in Japan, where there is a large number of hospital beds and a small number of physicians.

Previous studies [13–16] that developed prediction models of COVID-19 progression considered comorbidity status, blood cell count or ratios, and CRP levels. These factors [13–16] may help determine the need for hospitalization and oxygen supply.

The present scoring model should be verified in a validation cohort. We intend to perform prospective and multi-center studies to develop a model predicting the need for hospitalization in Japanese patients with COVID-19.

The present study has several limitations that must be considered when interpreting its findings. First, this study was retrospective and based on a single center. Second, because of the lack of a definite treatment policy for COVID-19 in Japan, treatment was selected according to the institution's treatment guideline. Third, the presented model was not tested in a validation cohort.

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Authorship

HK, TH, HS, TA, YT, and TN contributed to the conception and design of the study. HK, TH, HS, and TN contributed to data collection and analysis. HK, TH, HS, TA, YT, SH, HM, YM, YK, YH, SM, TT, and TN contributed to drafting and editing the manuscript. HK, TH, HS, HM, YM, YK, YH, SM, and TN revised the manuscript. HK, TH, HS, SH, TT, and NT supervised the study. HK, TH, HS, and TN conducted the statistical analyses. All authors read and approved the final manuscript. All authors met the ICMJE authorship criteria.

Declaration of competing interest

T.H. received honoraria and research funding as the primary investigator at this institution from Ono Pharmaceutical Co. Ltd. (Osaka, Japan); Lilly Japan Co. Ltd. (Hyogo, Japan); AstraZeneca Co. Ltd. (Osaka, Japan); Taiho Pharmaceutical Co. Ltd. (Tokyo, Japan); Chugai Pharmaceutical Co. Ltd. (Tokyo, Japan); and MSD Oncology Co. Ltd. (Tokyo, Japan). TH did not receive any honoraria or research funding associated with this study. None of the other authors have any financial conflicts of interest to disclose. The study was not funded by any organization.

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