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## Original Article

# The usefulness of a combination of age, body mass index, and blood urea nitrogen as prognostic factors in predicting oxygen requirements in patients with coronavirus disease 2019<sup>☆</sup>



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## ABSTRACT

**Introduction:** Risk factors for seriously ill coronavirus disease 19 (COVID-19) patients have been reported in several studies. However, to date, few studies have reported simple risk assessment tools for distinguishing patients becoming severely ill after initial diagnosis. Hence, this study aimed to develop a simple clinical risk nomogram predicting oxygenation risk in patients with COVID-19 at the first triage.

**Methods:** This retrospective study involved a chart review of the medical records of 84 patients diagnosed with COVID-19 between February 2020 and March 2021 at ten medical facilities. The patients were divided into requiring no oxygen therapy (non-severe group) and requiring oxygen therapy (severe group). Patient characteristics were compared between the two groups.

We utilized univariate logistic regression analysis to confirm determinants of high risks of requiring oxygen therapy in patients with moderate COVID-19.

**Results:** Thirty-five patients were in severe group and forty-nine patients were in non-severe group. In comparison with patients in the non-severe group, patients in the severe group were significantly older with higher body mass index (BMI), and had a history of hypertension and diabetes. Serum blood urea nitrogen (BUN), lactic acid dehydrogenase (LDH), and C-reactive protein (CRP) levels were significantly higher in the severe group. Multivariate analysis showed that older age, higher BMI, and higher BUN levels were significantly associated with oxygen requirements.

**Conclusions:** This study demonstrated that age, BMI, and BUN were independent risk factors in the moderate-to-severe COVID-19 group. Elderly patients with higher BMI and BUN require close monitoring and early treatment initiation.

## 1. Introduction

Since mid-December 2019, the outbreak of the novel coronavirus

disease (COVID-19) has suddenly emerged and spread worldwide. COVID-19 is an infectious disease induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is often severe enough to

<sup>☆</sup> ACE2, angiotensin-converting enzyme 2; AUC, area under the curve; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; COVID-19, coronavirus disease 19; CRP, C-reactive protein; IPPV, invasive positive-pressure ventilation; LDH, lactic acid dehydrogenase; MEWS, Modified Early Warning Score; SpO<sub>2</sub>, peripheral oxygen saturation; qCSI, quick COVID-19 Severity Index; qSOFA, Quick Sequential Organ Failure Assessment ROC, receiver operating characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

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require oxygenation in patients with older age, obesity, and health problems such as hypertension and diabetes [1–4].

At first diagnosis, physicians require quick selection of severe patients from a large number of COVID-19 patients based on physical assessment and limited information. Although COVID-19 is a potentially lethal disease, most patients do not require oxygen therapy and are relieved by symptomatic treatment [1]. Since the long-term outbreak of COVID-19 exhausts frontline health care workers, a simple and easy risk assessment that can detect patients requiring oxygen after the onset is essential to simplify triage. Previous studies have shown that older age, high body mass index (BMI), and other health conditions are risk factors for severe COVID-19 [2–4]. Identifying and evaluating these relevant factors and managing proper medical strategies would reduce complications of the disease by facilitating early diagnosis and treatment. Consequently, and the number of patients recovering from COVID-19 could increase. However, especially in the early period of onset, little is known about which factors were most relevant for detecting patients who become severe after first diagnosis.

Several studies have developed the clinical efficacy of physiological scoring systems for an early detection of high-risk COVID-19 patients. As predicting tool in-hospital mortality, the Modified Early Warning Score (MEWS) is one of these physiological scoring systems, and it includes variables including heart rate, systolic blood pressure, respiratory rate, body temperature, and state of consciousness [5]. A simpler scoring system is the quick COVID-19 Severity Index (qCSI), which includes variables such as respiratory rate, pulse oximetry, and oxygen flow rate [6]. qCSI focused on predicting respiratory failure within 24 h of admission. CURB-65 and A-DROP, a modified version of CURB-65, have been used to predict community-acquired pneumonia [7,8], and have also been reported as clinical predictors of COVID-19 [9]. The Quick Sequential Organ Failure Assessment (qSOFA), which can help physicians predict mortality, has also been reported as a risk-stratification tool for COVID-19 [10]. The 4C mortality score has been reported as a valid score for predicting post-hospital mortality [13]. However, regarding decisions about early treatment and intervention, a decision tool for distinguishing mild patients who do not require oxygen therapy from those with moderate disease who require oxygen therapy is more relevant at first diagnosis. The objective of this study was to develop a simple risk assessment tool to distinguish between patients who require oxygen therapy and those who do not require oxygen therapy at initial diagnosis.

## 2. Materials and methods

### 2.1. Study design

This was a case-control study to develop a prognostic model of early respiratory failure in patients with COVID-19 from 10 medical facilities (Shinshu University Hospital, Nagano Prefectural Shinshu Medical Center, Ina Central Hospital, Asama General Hospital, Okaya Municipal Hospital, Karuizawa Hospital, Shinshu Ueda Medical Center, Minami Nagano Medical Center Shinonoi General Hospital, Japanese Red Cross Society Suwa Hospital, and Matsumoto City Hospital) in Nagano Prefecture, Japan, based on the available data on their medical records.

### 2.2. Study participants and setting

This study was approved by our Institutional Review Board (approval number 4819, August 10, 2020). The requirement for written informed consent was waived due to using de-identified retrospective data. This research, on the other hand, used an opt-out consent model, which meant that patients could opt-out at any time and have their information deleted from the registry. We collected medical records of laboratory-confirmed hospitalized cases of COVID-19 between February 16, 2020 and March 21, 2021. Patients who required oxygen administration from the time of consultation were also included in this study.

COVID-19 diagnoses were confirmed by real-time reverse-transcription polymerase chain reaction assay for nasal or pharyngeal swab specimens. Each record was checked by two clinicians. In this study, salivary PCR was not used to diagnose any patients.

### 2.3. Measurement

Medical data of patient demographics, summarized medical histories, vital signs, outpatient medications, chest radiographs, and laboratory results at first diagnosis were collected. Additionally, data of respiratory support (high-flow nasal cannula, invasive positive-pressure ventilation [IPPV]), and total oxygen administration period were also collected. We defined severe respiratory illness in the setting of COVID-19 (severe vs. non-severe) as any COVID-19 patient meeting one of the following criteria: oxygen flow rate greater than or equal to 1 L/min; high-flow oxygenation; or IPPV.

Severity of COVID-19 at first diagnosis was assessed using the MEWS, qCSI, ADROP, CURB-65, and qSOFA scores. The MEWS was used to assess the following parameters: heart rate (beats/min), systolic blood pressure (mmHg), respiratory rate (breaths/min), body temperature (°C), and state of consciousness [5].

The qCSI predicting respiratory failure within 24 h of admission was defined as oxygen requirement of greater than 10 L/min by low-flow devices, high-flow devices, noninvasive or invasive ventilation, or death [6]. The quick qCSI is available at <https://covidseverityindex.org>.

The CURB-65 score included five parameters: advanced age ( $\geq 65$  years), dehydration (blood urea nitrogen  $> 19$  mg/dL), respiratory failure (respiratory rate  $\geq 30$ ), hypotension (systolic blood pressure  $\leq 90$  mmHg or diastolic blood pressure  $\leq 60$  mmHg), and confusion. One point was given for each of the CURB-65 components. Generally, the total score ranges from 0 to 5, with a score of 5 suggesting the poorest prognosis [7].

The ADROP scoring system predicted severe respiratory illness using the following parameters: advanced age ( $\geq 70$  years in men,  $\geq 75$  years in women), dehydration (blood urea nitrogen  $\geq 21$  mg/dL), respiratory failure (arterial oxygen saturation  $\leq 90\%$  or arterial oxygen pressure  $\leq 60$  torr), hypotension (systolic blood pressure  $\leq 90$  mmHg), and confusion. One point was given for each of the A-DROP components. The total score ranges from 0 to 5, with a score of 5 suggesting the poorest prognosis [8].

The qSOFA comprised three clinical parameters: systolic blood pressure  $\leq 100$  mmHg, respiratory rate  $\geq 22$  breaths/min, and altered mental status [10]. The qSOFA was created for evaluation of patients with sepsis. However, several recent studies have reported its effectiveness in predicting mortality in patients with different infectious diseases [11].

The 4C Mortality Score is comprised of Age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, degree of consciousness, urea level, and C reactive protein (score range 0–21 points) [13].

### 2.4. Data analysis

Descriptive data are reported as mean  $\pm$  standard deviation (SD) for continuous variables of normal distribution, median [25th quartile, 75th quartile] for continuous variables of non-normal distribution, and percentage for categorical data. Continuous data of normal distribution were tested using the *t*-test, continuous data of non-normal distribution were tested using the Mann-Whitney *U* test for non-normal distribution, and categorical variables were compared using either the chi-square test of Fisher's exact test (when the expected value  $< 0.05$  in one cell), as appropriate. Univariate logistic regression analysis followed by multivariate analysis was used to identify the determinants of a high risk of moderate COVID-19 requiring oxygen therapy. From the variables that were significant by univariate analysis, we narrowed down the 3 variables (Age, BMI, serum BUN) by using the stepwise method. We

confirmed selection of these variables was correct based on previous literature [17,22–24].

The ability of each risk score and biomarker to discriminate between non-severe and severe patients was evaluated by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) and its 95% confidence interval (CI) (95% CI). Statistical analysis was performed using a Windows compatible software program (StatFlex version 7; Artech Co. Ltd, Osaka, Japan) and the nomogram was plotted using another software program (BellCurve for Excel (version 3.21); Social Survey Research Information Co., Ltd, Japan). Statistical significance was set at  $P < 0.05$ .

### 3. Results

#### 3.1. Baseline characteristics

During the investigation period, 104 patients met the diagnostic criteria for COVID-19. Excluding 20 patients with missing BMI data, 84 cases were evaluated. In total, the mean age was  $54.4 \pm 18.4$ , and 51 patients (60.7%) were men. Baseline characteristics are listed in Table 1. In terms of consciousness, all the survivors were alert. Only one non-survivor had an altered state of consciousness in response to verbal stimuli.

#### 3.2. Comparison of clinical data between the non-severe and severe groups

Thirty-five patients were in severe group and forty-nine patients were in non-severe group. The characteristics with significant difference, expressed in terms of the severe group versus the non-severe group, were as follows: ages of  $65.2 \pm 12.2$  years versus  $46.6 \pm 18.3$  years, BMI of  $25.2 \pm 4.6$  versus  $23.0 \pm 3.5$ , Brinkman index of  $604 \pm 572$  versus  $161 \pm 282$ , peripheral oxygen saturation ( $SpO_2$ ) of  $92.7 \pm 4.7$  versus  $96.2 \pm 1.9$ . In the severe group, the median duration from the onset date to the start date of oxygen administration was 5 (IQR, 3–8) days. In the severe group, 13 patients required high-flow nasal therapy, and 11 patients were intubated. One patient died in the severe group (1.0%). In the severe group, all patients developed decrease in  $SpO_2$  to the extent that oxygen administration is required. The signs and symptoms on admission showed significant differences regarding the severe group versus the non-severe group were as follows: fever in 25 patients (71.4%) versus 23 patients (46.9%), fatigue in 19 patients (54.3%) versus 9 patients (18.4%), dyspnea in 11 (31.4%) versus 2 (4.1%), respectively. In Table 1, we also report existing underlying diseases between the non-severe and severe groups. The existing underlying diseases with significant differences between the severe and non-severe groups were as follows: hypertension in 19 patients (54.3%) versus 4 patients (8.2%), and 15 patients (42.9%) versus diabetes in 3 (8.2%).

#### 3.3. Comparison of laboratory findings between the non-severe and severe groups

Laboratory test results showed that the severe group presented with significantly lower levels of lymphocytes ( $911/\mu\text{L}$  versus  $1330/\mu\text{L}$ ), platelet counts ( $16.2 \times 10^4/\mu\text{L}$  versus  $20.6 \times 10^4/\mu\text{L}$ ), and albumin (3.6 g/dL versus 4.2 g/dL) compared with the non-severe group.

The severe group also presented with significantly higher levels of aspartate aminotransferase (41.0 IU/L versus 23.0 IU/L), alanine aminotransferase (36.0 IU/L versus 21.0 IU/L), lactic acid dehydrogenase (LDH) (287.0 IU/L versus 183.0 IU/L), blood urea nitrogen (BUN) (16.9 mg/dL versus 12.3 mg/dL), creatinine (0.91 mg/dL versus 0.73 mg/dL), C-reactive protein (CRP) (2.3 mg/dL versus 0.3 mg/dL), and sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6) (273 U/L versus 191 U/L).

**Table 1**  
Demographic and clinical characteristics between the patient groups.

Demographics	Patients, No.(%)			p-value (Severe vs Non-severe)
	All patients (n = 84)	Severe (n = 35)	Non-severe (n = 49)	
Age, mean (SD)	54.4 (18.4)	65.2 (12.2)	46.6 (18.3)	< 0.001
≥65, n (%)	30 (35.7%)	19 (54.3)	11 (22.4)	< 0.05
BMI, mean (SD)	24.0 (4.1)	25.2 (4.6)	23.0 (3.5)	< 0.05
Male, n (%)	51 (60.7%)	23 (65.7%)	28 (57.1%)	0.43
Female, n (%)	33 (39.3%)	12 (34.3%)	21 (42.9%)	0.44
Smoker	43 (51.2%)	17 (48.6%)	26 (53.0%)	0.68
Brinkman index, mean (SD)	336 (469)	604 (572)	161 (282)	< 0.05
<b>Comorbidities</b>				
Hypertension, n (%)	23 (27.4%)	19 (54.3%)	4 (8.2%)	< 0.001
Cardiovascular disease, n (%)	4 (4.8%)	2 (5.7%)	2 (4.1%)	1.00
Arrhythmia, n (%)	3 (3.6%)	3 (8.6%)	0 (0.0%)	0.07
Liver disease, n (%)	2 (2.4%)	2 (5.7%)	0 (0.0%)	0.17
Malignancy, n (%)	5 (6.0%)	3 (8.6%)	2 (4.1%)	0.64
COPD, n (%)	3 (3.6%)	2 (5.7%)	1 (2.0%)	0.57
Asthma, n (%)	5 (6.0%)	2 (5.7%)	3 (6.1%)	1.00
Diabetes, n (%)	19 (22.6%)	15 (42.9%)	4 (8.2%)	< 0.001
Chronic renal disease, n (%)	1 (1.2%)	1 (2.9%)	0 (0.0%)	0.41
Rheumatoid arthritis, n (%)	1 (1.2%)	0 (0.0%)	1 (2.0%)	1.00
<b>Oxygenation requirement and respiratory support</b>				
Days from the onset date to the start date of oxygen administration median (IQR)		5 (3, 8)		
$SpO_2$ at start O2 supplement, median (IQR)		90 (78–90)		
$SpO_2$ at finish O2 supplement, median (IQR)		95 (90–95)		
$SpO_2$ at last physical examination, median (IQR)		96 (90–96)		
High-flow nasal therapy, n (%)		13 (37.1%)		
Intubation, n (%)		11 (31.4%)		
Death, n (%)	1 (1.0%)	1 (3.0%)	0 (0.0%)	
<b>Signs and Symptoms on admission</b>				
Asymptomatic	7 (8.3%)	0 (0.0%)	7 (14.3%)	
Fever	48 (57.1%)	25 (71.4%)	23 (46.9%)	< 0.05
Chills	1 (1.2%)	0 (0.0%)	1 (2.0%)	1.00
fatigue	28 (33.3%)	19 (54.3%)	9 (18.4%)	< 0.001
arthralgia	8 (9.5%)	4 (11.4%)	4 (8.2%)	0.46
headache	9 (10.7%)	3 (8.6%)	6 (12.2%)	0.80
Sore throat	23 (27.4%)	7 (20.0%)	16 (33.3%)	0.25
Runny nose /nasal congestion	12 (14.3%)	3 (8.6%)	9 (18.4%)	0.34
dysgeusia	11 (13.1%)	3 (8.6%)	8 (16.7%)	0.34
smell disturbance	12 (14.3%)	5 (14.3%)	7 (14.3%)	1.00
cough	29 (34.5%)	13 (37.1%)	16 (32.7%)	0.67
Sputum	12 (15.5%)	8 (22.9%)	5 (10.2%)	0.11

(continued on next page)

Table 1 (continued)

Demographics	Patients, No.(%)			
	All patients (n = 84)	Severe (n = 35)	Non-severe (n = 49)	p-value (Severe vs Non-severe)
Dyspnea	13 (15.5%)	11 (31.4%)	2 (4.1%)	< 0.001
Nausea and vomiting	5 (6.0%)	3 (8.6%)	2 (4.1%)	0.64
diarrhea	6 (7.1%)	4 (11.4%)	2 (4.1%)	0.22
<b>Laboratory findings at admission, median(IQR)</b>				
WBC, /μL	4950 (3900, 6800)	4600 (3735, 6755)	5000 (4072, 10,036)	0.56
Lym, %	22.8 (17.0, 32.7)	20.7 (13.2, 27.4)	26.3 (19.5, 34.3)	< 0.05
Lym, /μL	1116 (759, 1529)	911 (660, 1151)	1330 (890, 1671)	< 0.05
Hb, g/dL	14.4 (13.6, 15.9)	14.4 (13.6, 16.4)	14.4 (13.7, 15.5)	0.48
Plt, × 10 <sup>4</sup> /μL	18.9 (14.7, 25.2)	16.2 (13.6, 20.4)	20.6 (16.4, 26.8)	< 0.05
TP, g/dL	7.0 (6.7, 7.5)	6.9 (6.6, 7.3)	7.1 (6.7, 7.7)	0.13
Alb, g/dL	4.0 (3.6, 4.3)	3.6 (3.3, 3.9)	4.2 (3.9, 4.4)	< 0.05
AST, IU/L	28 (21, 42)	41.0 (29, 55)	23.0 (19.8, 30.0)	< 0.05
ALT, IU/L	26 (17, 39)	36.0 (23.3, 47.8)	21.0 (14.8, 33.0)	< 0.05
LDH, IU/L	218 (174, 296)	287.0 (215.5, 384.0)	183.0 (169.0, 228.5)	< 0.001
T-Bil, mg/dL	0.5 (0.4, 0.7)	0.51 (0.40, 0.75)	0.50 (0.40, 0.64)	0.56
BUN, mg/dL	13.3 (11.2, 17.1)	16.9 (13.2, 21.0)	12.3 (9.6, 13.9)	< 0.001
Cre, mg/dL	0.81 (0.64, 0.97)	0.91 (0.68, 1.09)	0.73 (0.60, 0.89)	< 0.05
UA, mg/dL	5.0 (4.0, 6.2)	5.3 (4.2, 6.1)	5.0 (3.7, 6.2)	0.61
CRP, mg/dL	0.9 (0.2, 3.4)	2.3 (1.3, 8.2)	0.3 (0.0, 0.9)	< 0.001
KL-6, U/L	230 (191, 381)	273 (216, 422)	191 (130, 287)	< 0.001
Feritin, μg/L	340 (219, 754) (n = 18)	407.5 (251.0, 775.0) (n = 14)	172.7 (n = 4)	
D-dimer, nmol/L	0.5 (0.3, 1.1)	1.0 (0.5, 1.6)	0.5 (0.1, 0.5)	
<b>Treatment</b>				
Baloxavir marboxil		1 (2.9%)	3 (6.1%)	
loponavir, ritonavir.		4 (11.4%)	0 (0.0%)	
Favipiravir		17 (48.6%)	20 (40.8%)	
Remdesivir		15 (42.9%)	0 (0.0%)	< 0.001
Methylprednisolone		23 (65.7%)	5 (10.2%)	< 0.001
Dexamethasone		18 (51.4%)	1 (2.0%)	< 0.001
Ciclesonide		10 (28.6%)	18 (36.7%)	
Prednisolone		1 (2.9%)	1 (2.0%)	
Tocilizumab		9 (25.7%)	0 (0.0%)	
heparin		12 (34.3%)	1 (2.0%)	
nafamostat		7 (20.0%)	5 (10.2%)	
<b>Imaging studies</b>				
Abnormal Chest X-rays results		(n = 29)	(n = 34)	

Table 1 (continued)

Demographics	Patients, No.(%)			
	All patients (n = 84)	Severe (n = 35)	Non-severe (n = 49)	p-value (Severe vs Non-severe)
Bilateral GGO	19 (22.6%)	8 (23.5%)	8 (23.5%)	
Consolidation no abnormal shadow	11 (13.1%)	2 (5.9%)	28 (71.8%)	
<b>Abnormal Chest Computed Tomography results</b>				
Bilateral	26 (30.9%)	18 (51.4%)	18 (41.9%)	
GGO	35 (41.7%)	31 (88.6%)	31 (72.1%)	
Consolidation	14 (16.7%)	4 (11.4%)	4 (9.3%)	
<b>Vital signs</b>				
systolic blood pressure (mmHg)	128 (121, 140)	128 (120, 141)	127 (123, 141)	0.88
diastolic blood pressure (mmHg)	81 (72, 92)	80 (72, 92)	82 (73, 91)	0.75
heart rate (beat per minute)	81 (75, 96)	86 (72, 98)	80 (75, 92)	0.81
respiratory rate (per minute)	18 (16, 20)	20 (16, 22)	18 (16, 20)	0.07
temperature (°C)	36.9 (36.5, 37.6)	37.0 (36.5, 37.8)	36.8 (36.5, 37.4)	0.35
SpO <sub>2</sub> (%)	96 (94, 97)	94 (90, 96)	97 (95, 98)	< 0.001
MEWS	1 (1, 2)	1 (1, 1)	1 (1, 1)	
qCSI	0 (0, 0.25)	0 (0, 0)	0 (0, 0)	
CURB-65	1 (0, 1)	0 (0, 0)	0 (0, 0)	
ADROP	1 (0, 1)	0 (0, 0)	0 (0, 0)	
qSOFA	0 (0, 1)	0 (0, 0)	0 (0, 0)	
4C mortality score	8 (4, 12)	3 (1, 5)	3 (1, 5)	< 0.001

Note: Bold values indicate statistical significance. Abbreviations: Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; Cre, creatinine; GGO, ground glass opacity; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6; Lym, lymphocyte; LDH, lactate dehydrogenase; Plt, platelet; T-Bil, total bilirubin; UA, uric acid; WBC, white blood cell.

3.4. Treatments

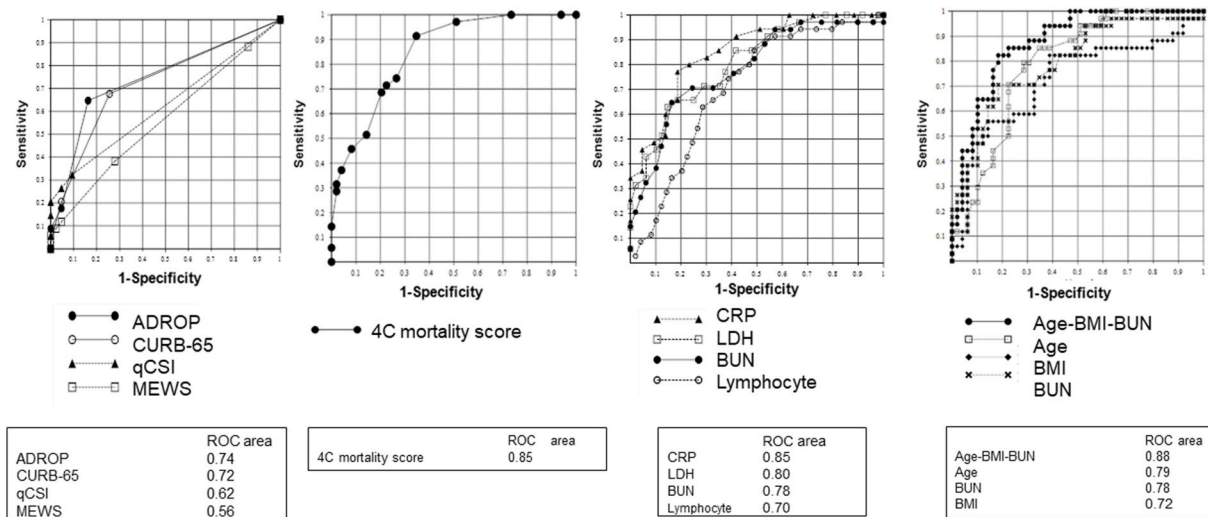
Favipiravir was the most frequently used antiviral drug in the initial treatment regimen in both the severe and non-severe groups. Adjuvant corticosteroid therapy was significantly more frequent in the severe group than in the non-severe group.

3.5. Prognostic ability of each scoring system, laboratory parameters to estimate oxygen requirement

As shown in Table 1, the median [25th quartile, 75th quartile] of the MEWS of the severe group versus the non-severe group were 1 [1,2] and 1 [1,1], and that of the qCSI was 0 [0, 0.3] and 0 [0, 0], respectively, and that of the ADROP was 1 [0, 1] and 0 [0, 0], and that of the CURB-65 was 1 [0, 1] and 0 [0, 0], and that of the qSOFA was 0 [0, 1] and 0 [0, 0], and that of the 4C mortality score was 8 [4,12] and 3 [1,5]. In the severe group, 4C mortality score was significantly higher than in the non-severe group. Because almost all patients showed 0 points, the qSOFA was eliminated from the ROC analysis.

Fig. 1 shows the AUC according to four scoring systems (the MEWS, qCSI, CURB-65, and ADROP) and four laboratory parameters (CRP, LDH, BUN, lymphocytes). The AUC (±SE) of each scoring system were: 0.74 (±0.059) for the ADROP, 0.72 (±0.060) for the CURB-65, 0.62 (±0.065) for the qCSI, and 0.56 (±0.067) for the MEWS. The AUC (±SE)





**Fig. 1.** The receiver operating characteristic (ROC) curve analysis of four scoring systems and four laboratory parameters of COVID-19 patients. Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase.

of 4C mortality score was 0.85 ( $\pm 0.040$ ). The AUC ( $\pm$ SE) of each laboratory parameter were 0.85 ( $\pm 0.041$ ) for CRP, 0.80 ( $\pm 0.046$ ) for LDH, 0.78 ( $\pm 0.050$ ) for BUN, and 0.70 ( $\pm 0.057$ ) for lymphocytes. The optimal cut off values to assess severity of COVID-19 by the Youden’s index method were 1.1 mg/dL for CRP, 258 IU/L for LDH, 14.0 mg/dL for BUN, and 1175/ $\mu$ L for lymphocytes. The AUC of multivariate logistic regression analysis with age, BMI, and BUN as variables was 0.88.

**3.6. Prognostic factors for oxygen requirement and nomogram construction**

Univariate logistic regression analysis showed that high age (Odd ratio: 1.074; 95% CI: 1.038–1.112;  $p = 0.00005$ ), higher BMI (Odd ratio: 1.225; 95% CI: 1.027–1.298;  $p = 0.01631$ ), lower lymphocytes (Odd ratio: 0.999; 95% CI: 0.998–1.000;  $p = 0.00379$ ), lower serum albumin (Odd ratio: 0.999; 95% CI: 0.998–1.000;  $p = 0.00379$ ), higher serum LDH (Odd ratio: 1.016; 95% CI: 1.008–1.024;  $p = 0.00006$ ), higher serum BUN (Odd ratio: 1.271; 95% CI: 1.112–1.453;  $p = 0.00044$ ), and higher CRP (Odd ratio: 1.827; 95% CI: 1.287–2.594;  $p = 0.00076$ ) were associated with a high risk of oxygen requirement (Table 2).

Multivariate analysis showed that higher age (odds ratio: 1.054; 95% CI: 1.019–1.171;  $p = 0.007$ ), higher BMI (odds ratio: 1.201; 95% CI: 1.035–1.588;  $p = 0.013$ ), higher serum BUN (odds ratio: 1.178; 95% CI: 1.005–1.586;  $p = 0.018$ ) were independently associated with high risk of oxygen requirement.

Based on the final multivariate model, three prognostic factors including age, BMI, and BUN were combined to construct a nomogram for oxygen requirement. The probability of oxygen requirement after first diagnosis was calculated based on the bottom point scale of the nomogram (Fig. 2).

**4. Discussion**

To date, this is the first report to evaluate associations between the predictability of oxygen requirement after COVID-19 onset and health conditions (age, BMI, and blood laboratory data) obtained at initial diagnosis. We found that age, BMI, and BUN were the key host factors for respiratory illness in patients with COVID-19.

Regarding severe COVID-19, previous studies have reported that major risk factors included age, male sex, obesity, smoking, and comorbid chronic conditions such as hypertension and diabetes mellitus [1–3,12]. In line with these reports, age, BMI, Brinkman index, prevalence of hypertension, and diabetes were significantly higher in the

**Table 2**

Univariate and multivariate logistic regression analyses of age, BMI, brink man index and laboratory data for predicting oxygen requirement for patients with coronavirus disease 2019.

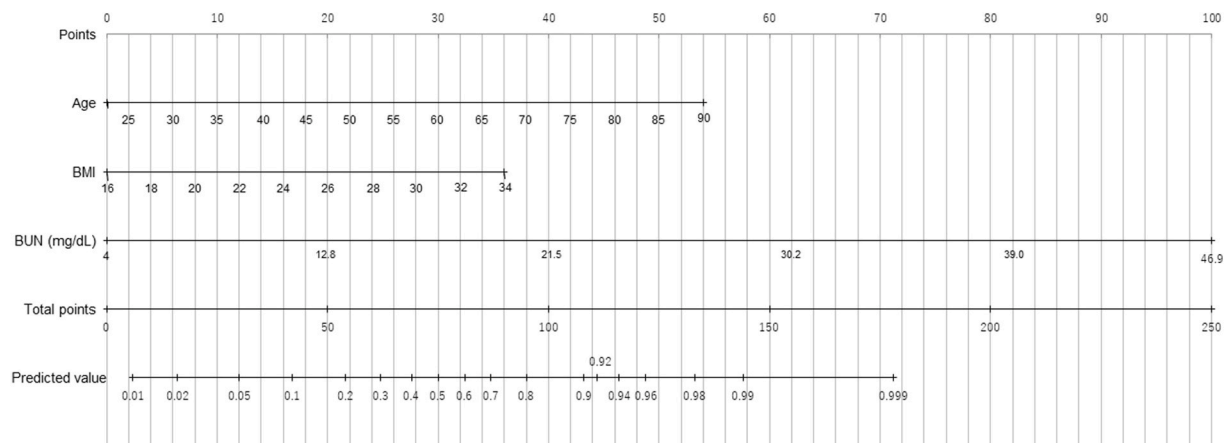
Univariate logistic regression analysis			
Variable	Odds ratio	95% CI	p value
Age (years)	1.074	1.038–1.112	< 0.001
BMI	1.225	1.027–1.298	< 0.001
Brinkman index (pack-years)	1.002	1.001–1.004	0.007
Laboratory data			
WBC (/ $\mu$ L)	1.000	1.000–1.000	0.881
Lym (/ $\mu$ L)	0.999	0.998–1.000	<b>0.045</b>
Hb (g/dL)	1.060	0.811–1.385	0.670
Serum Alb (g/dL)	0.158	0.056–0.446	< 0.001
Serum T-Bil (mg/dL)	3.745	0.676–20.756	0.130
Serum LDH (IU/L)	1.016	1.008–1.024	< 0.001
Serum BUN(mg/dL)	1.271	1.112–1.453	< 0.001
Serum CRP (mg/dL)	1.827	1.287–2.594	< 0.001
Multi logistic regression analysis			
Variable	Odds ratio	95% CI	p value
Age (years)	1.054	1.019–1.171	<b>0.007</b>
BMI	1.201	1.035–1.588	<b>0.013</b>
Serum BUN(mg/dL)	1.178	1.005–1.586	<b>0.018</b>

Note: Bold values indicate statistical significance. Abbreviations: Alb, albumin; BMI, body mass index; BUN, blood urea nitrogen; Lym, lymphocyte; LDH, lactate dehydrogenase; Plt, platelet; T-Bil, total bilirubin; UA, uric acid; WBC, white blood cell.

severe group than in the non-severe group.

In this study, univariate logistic regression analysis revealed a significant difference between the non-severe and severe groups in terms of age, BMI, lymphocytes, LDH, BUN, and CRP levels. Some other studies had assessed prognosis factors: Knight et al. evaluated 35,463 patients and reported the 4C mortality score that consisted of age, sex, number of comorbidities, SpO<sub>2</sub>, Glasgow coma scale score, BUN, and CRP [13]. Liang et al. also reported a risk score consisting of chest X-ray abnormalities, age, hemoptysis, dyspnea, sate of unconsciousness, number of comorbidities, cancer history, neutrophil/lymphocytes, LDH, and direct bilirubin. To date, most studies have focused on indices of laboratory examinations, such as D-dimer, lymphocytes, and LDH [14]. Of note, aging is a prominent risk factor for severe disease and death from COVID19 [15,16].

Based on the multi-logistic regression analysis, serum BUN was found to be an independent factor of the need for oxygen therapy after COVID-19 onset. In this study, we found elevated BUN and creatinine



**Fig. 2.** Nomogram for predicting oxygen requirements in COVID-19 patients after admission. Prognostic factors were listed on the left side and right axis for each of them will help determine the point for COVID-19 patients according to their individual clinical information. The sum of these points will be confirmed and dotted in the axis of Total points. A line is drawn downward to the Predicted value axes from total points to determine the probability of oxygen requirement after first diagnosis. Abbreviation: BUN, blood urea nitrogen.

levels, in line with the report by Marya et al. [17]. Ok et al. also reported that the BUN/creatinine ratio was an independent predictor of high-risk COVID-19 [18]. As a biomarker of dehydration, BUN is a component of other risk scores, such as the ADROP and CURB-65. From another point of view, BUN is also the main parameter showing kidney function. SARS-CoV-2 enters cells using angiotensin-converting enzyme 2 (ACE2) receptors [19]. Using single-cell RNA sequencing, a previous report suggested that ACE2 was highly expressed in the kidneys and lungs [20]. Autopsy data of COVID-19 positive patients in Wuhan showed direct infiltration of tubular epithelium cells [21]. SARS-CoV-2 can cause passive reabsorption of BUN by activating the renin-angiotensin-aldosterone system [21]. During the first diagnosis period, BUN may be a simple but key biomarker for detecting severe COVID-19 with dehydration or renal failure.

In this study, BMI was another independent factor for the need for oxygenation after COVID-19 onset. A systematic review and meta-analysis revealed that obesity worsens COVID-19 [22–24]. Obesity and diabetes have increased awareness of their impact on patients with COVID-19 [25].

In ROC curve analyses, BUN, LDH, CRP, and lymphocyte counts were acceptable predictive values for the predictability of oxygen requirement after COVID-19 onset. Compared with only laboratory parameters, the advantages of the age-BMI-BUN combination are its more suitable physiological parameters allowing stratification of patients with a higher accuracy.

This study has several limitations. First, it was a multicenter retrospective study with a small number of patients. Additional prospective studies with larger sample sizes should be performed to confirm our results. Second, we used various therapeutic agents after diagnosis of COVID-19, some at a significantly different frequency in the mild and moderate-to-severe groups. Although no drug has been established to be effective in patients with COVID-19, it is possible that the drugs we used have had an impact on disease progression. Third, because we could not collect sufficient numbers of patients, we could not address clinical differences between patients required HFNC and patients required IPPV in the severe group.

## 5. Conclusions

This study demonstrated that age, BMI, and BUN were independent risk factors in the moderate-to-severe COVID-19 group. Patients with older age, high BMI, and higher BUN require close monitoring to start early treatment.

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## Author statement

All authors met the ICMJE authorship criteria. NG and YW designed the study. NG, YW, Y I, J A, M K, A U, Y K, M Y, A M, T H, G I, and Y Y collected the data. NG, YW, and M H analyzed and interpreted the data. NG and YW wrote the manuscript. All authors reviewed the manuscript.

## Declaration of competing interest

None.

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