[1]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

Goto Norihiko [a], Yosuke Wada [a*], Yuichi Ikuyama [a], Jumpei Akahane [a], Makoto Kosaka [c], Atsuhito Ushiki [a], Yoshiaki Kitaguchi [a], Masanori Yasuo [b], Hiroshi Yamamoto [a], Akemi Matsuo [d], Tsutomu Hachiya [e], Gen Ideura [f], Yoshitaka Yamazaki [c], Masayuki Hanaoka [a]

[a] First Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Nagano, 390-8621, Japan

[b] Departments of Clinical Laboratory Sciences, Shinshu University School of Health Sciences, Matsumoto, Nagano, 390-8621, Japan

[1] 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_2, 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

[c] Center of Infectious Diseases, Nagano Prefectural Shinshu Medical Center, 1332, Suzaka, Suzaka City, Nagano, 382-8577, Japan

[d] Department of Respiratory Medicine, Minaminagano Medical Center, Shinonoi General Hospital, 666-1 Ai, Shinonoi, Nagano City, Nagano, 388-8004, Japan

[e] Department of Respiratory Medicine, Japanese Red Cross Society Suwa Hospital, 5-11-50, Kogandori, Suwa City, Nagano, 392-8510, Japan

[f] Department of Respiratory Medicine, National Hospital Organization Shinshu Ueda Medical Center, 386-8610, Japan

* Correspondence: Yosuke Wada, First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. Telephone/Fax 0263-37-2631/0263-36-3722.

E-mail address: yosuke@shinshu-u.ac.jp

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.

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 ware 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.

Keywords: Aged, Body mass index, Blood urea nitrogen, COVID-19, Diabetes

mellitus, Nomograms

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 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 focued on predicting respiratory failure within 24 hours 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-contol 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 hours 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 (≥65 years), dehydration (blood urea nitrogen >19 mg/dL), respiratory failure (respiratory rate ≥30), hypotension (systolic blood pressure ≤90 mmHg or diastolic blood pressure ≤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 (≥70 years in men, ≥75 years in women), dehydration (blood urea nitrogen ≥21 mg/dL), respiratory failure (arterial oxygen saturation ≤ 90% or arterial oxygen pressure ≤60 torr), hypotension (systolic blood pressure ≤ 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 ≤100 mmHg, respiratory rate ≥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 comprise 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 ± 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 oderate 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 ± 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 ware 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 ± 12.2 years versus46.6 ± 18.3 years, BMI of 25.2 ± 4.6 versus 23.0 ± 3.5, Brinkman index of 604 ± 572 versus 161 ± 282, peripheral oxygen saturation (SpO_2) of 92.7 ± 4.7 versus96.2 ± 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 SpO2 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 /μL versus 1330 /μL), platelet counts (16.2 $\times 10^4$/μL versus 20.6 $\times 10^4$/μL), 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).

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) of 4C mortality score was 0.85(± 0.040) .The AUC (± SE) of each laboratory parameter were 0.85 (± 0.041) for CRP, 0.80 (± 0.046) for LDH, 0.78 (± 0.050) for BUN, and 0.70 (± 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 /μL 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: 1.154; 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.

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 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 35463 patients and reported the 4C mortality score that consisted of age, sex, number of comorbidities, SpO_2, 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 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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References

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30. PMID: 31986264; PMC ID: PMC7159299.

[2] Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy 2021;76:428–55. doi: 10.1111/all.14657. Epub 2020 December 4. PMID: 33185910.

[3] Hernández-Galdamez DR, González-Block MÁ, Romo-Dueñas DK, Lima-Morales R, Hernández-Vicente IA, Lumbreras-Guzmán M, et al. Increased risk of hospitalization and death in patients with COVID-19 and pre-existing noncommunicable diseases and modifiable risk factors in Mexico. Arch Med Res 2020;51:683–9. doi: 10.1016/j.arcmed.2020.07.003. Epub 2020 July 22. PMID: 32747155, PMCID: PMC7375298.

[4] Rashedi J, Mahdavi Poor B, Asgharzadeh V, Pourostadi M, Samadi Kafil H,

Vegari A, et al. Risk factors for COVID-19. Infez Med 2020;28:469–74. PMID: 33257620.

[5] Hu H, Yao N, Qiu Y. Comparing rapid scoring systems in mortality prediction of critically ill patients with novel coronavirus disease. Acad Emerg Med 2020;27:461–8. doi: 10.1111/acem.13992. Epub 2020 May 21. PMID: 32311790, PMCID: PMC7264631.

[6] Haimovich AD, Ravindra NG, Stoytchev S, Young HP, Wilson FP, van Dijk D, et al. Development and validation of the quick COVID-19 severity index: A prognostic tool for early clinical decompensation. Ann Emerg Med 2020;76:442–53. doi: 10.1016/j.annemergmed.2020.07.022. Epub 2020 July 21. PMID: 33012378, PMCID: PMC7373004.

[7] Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 2003;58:377–82. doi: 10.1136/thorax.58.5.377, PMID: 12728155, PMCID: PMC1746657.

[8] Miyashita N, Matsushima T, Oka M, Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: An update and new recommendations. Intern Med 2006;45:419–28. doi: 10.2169/internalmedicine.45.1691. Epub 2006 May 1. PMID: 16679695.

[9] Fan G, Tu C, Zhou F, Liu Z, Wang Y, Song B, et al. Comparison of severity scores for COVID-19 patients with pneumonia: A retrospective study. Eur Respir J 2020;56:2002113, doi: 10.1183/13993003.02113-2020, PMID: 32675205, PMCID: PMC7366179.

[10] Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Am J Emerg Med 2020;38:2074–80. doi: 10.1016/j.ajem.2020.07.019. Epub 2020 July 12. PMID: 33142178, PMCID: PMC7354270.

[11] Jiang J, Yang J, Mei J, Jin Y, Lu Y. Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: A meta-analysis. Scand J Trauma Resusc Emerg Med 2018;26:56. doi: 10.1186/s13049-018-0527-9, PMID: 29996880, PMCID: PMC6042435.

[12] Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19. JAMA Netw Open. 2020 Dec 1;3:e2029058. doi: 10.1001/jamanetworkopen.2020.29058. Erratum in: JAMA Netw Open. PMID: 33301018; PMC ID: PMC7729428 2021;4:e2036103. DOI: 10.1001/jamanetworkopen.2020.36103.

[13] Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Development and validation of the 4C Mortality Score. BMJ 2020;370:m3339. doi: 10.1136/bmj.m3339. Erratum in: BMJ. PMID: 32907855; PMC ID: PMC7116472 2020;371:m4334.

[14] Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med 2020;180:1081–9. doi: 10.1001/jamainternmed.2020.2033, PMID: 32396163, PMCID: PMC7218676.

[15] Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect

2020;80:e14–8. doi: 10.1016/j.jinf.2020.03.005. Epub 2020 March 27. PMID: 32171866, PMCID: PMC7102640.

[16] Chen Y, Klein SL, Garibaldi BT, Li H, Wu C, Osevala NM, et al. Aging in COVID-19: Vulnerability, immunity and intervention. Ageing Res Rev 2021;65:101205. doi: 10.1016/j.arr.2020.101205. Epub 2020 October 31. PMID: 33137510, PMCID: PMC7604159.

[17] AlSamman M, Caggiula A, Ganguli S, Misak M, Pourmand A. Non-respiratory presentations of COVID-19, a clinical review. Am J Emerg Med 2020;38:2444–54. doi: 10.1016/j.ajem.2020.09.054. Epub 2020 September 24. PMID: 33039218, PMCID: PMC7513760.

[18] Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive values of blood urea nitrogen/creatinine ratio and other routine blood parameters on disease severity and survival of COVID-19 patients. J Med Virol 2021;93:786–93. doi: 10.1002/jmv.26300. Epub 2020 July 22. PMID: 32662893, PMCID: PMC7405288.

[19] Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal

histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98:219–27. doi: 10.1016/j.kint.2020.04.003. Epub 2020 April 9. PMID: 32327202, PMCID: PMC7194105.

[20] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020;14:185–92. doi: 10.1007/s11684-020-0754-0. Epub 2020 March 12. PMID: 32170560, PMCID: PMC7088738.

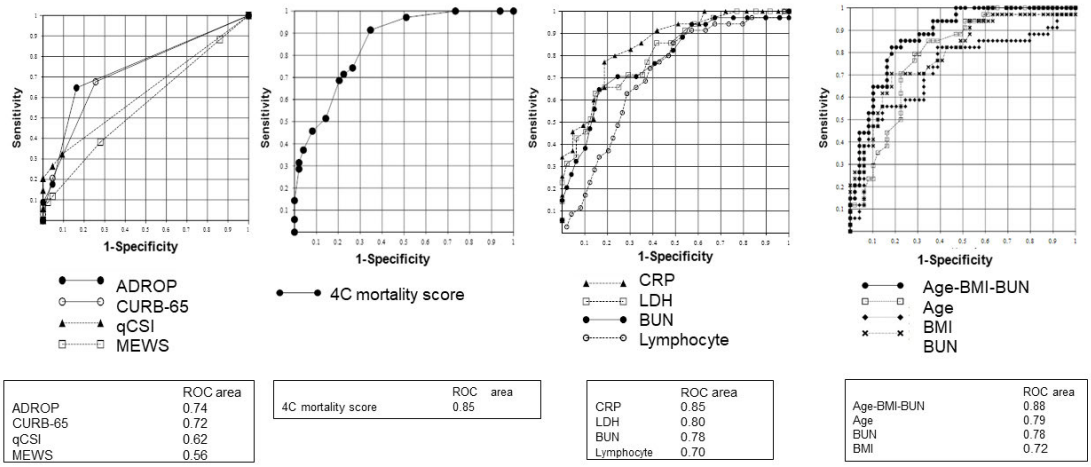
[21] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829–38. doi: 10.1016/j.kint.2020.03.005. Epub 2020 March 20. PMID: 32247631, PMCID: PMC7110296.

[22] Aghili SMM, Ebrahimpur M, Arjmand B, Shadman Z, Pejman Sani M, Qorbani M, et al. Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: A review and meta-analysis. Int J Obes (Lond) 2021:1–19. doi: 10.1038/s41366-021-00776-8 [Epub ahead of print]. PMID: 33637951, PMCID: PMC7909378.

[23] Du Y, Lv Y, Zha W, Zhou N, Hong X. Association of body mass index (BMI) with critical COVID-19 and in-hospital mortality: A dose–response meta-analysis. Metabolism 2021;117:154373. doi: 10.1016/j.metabol.2020.154373. Epub 2020 September 16. PMID: 32949592, PMCID: PMC7493748.

[24] Zhao X, Gang X, He G, Li Z, Lv Y, Han Q, Wang G. Obesity increases the severity and mortality of influenza and COVID-19: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2020;11:595109. doi: 10.3389/fendo.2020.595109, PMID: 33408692, PMCID: PMC7779975.

[25] Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev 2021;37:e3377. doi: 10.1002/dmrr.3377. Epub 2020 July 20. PMID: 32588943, PMCID: PMC7361201.



	ROC area
ADROP	0.74
CURB-65	0.72
qCSI	0.62
MEWS	0.56

	ROC area
4C mortality score	0.85

	ROC area
CRP	0.85
LDH	0.80
BUN	0.78
Lymphocyte	0.70

	ROC area
Age-BMI-BUN	0.88
Age	0.79
BUN	0.78
BMI	0.72

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.

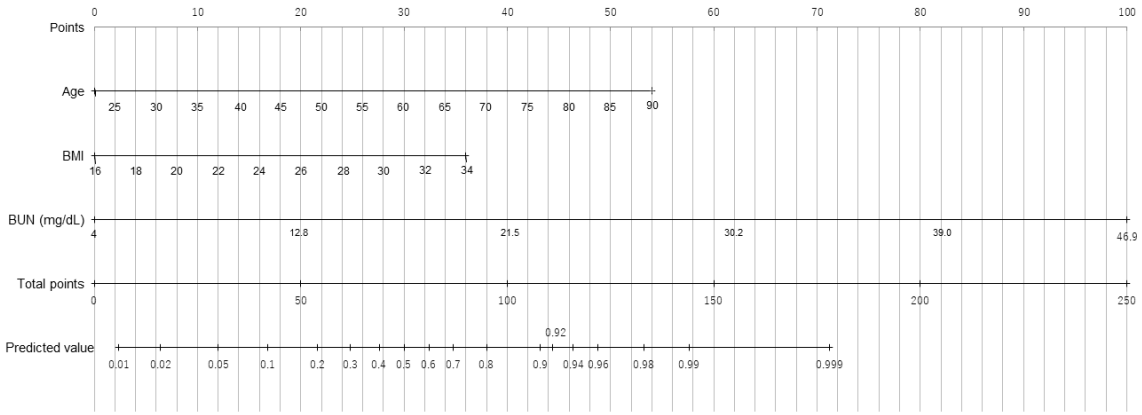


Fig. 2. Nomogram for predicting oxygen requirements in COVID-19 patients after admission. Prognostic factors were listed on the left side and right axis for each of them will help determine the point for COVID-19 patients according to their individual clinical information. The sum of these points will 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

Table 1. Demographic and clinical characteristics between the patient groups

Demographics	Patients, No.(%)			
	All patients(n=84)	Severe(n=35)	Non-severe(n=49)	*p*-value(Severe vs Non-severe)
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**
Comorbidities				
Hypertension, n (%)				
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
Oxygenation requirement				

and respiratory support				
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%)	
Signs and Symptoms on admission				
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
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
Laboratory findings at admission, median(IQR)				
WBC, /μL	4950 (3900, 6800)	4600 (3735, 6755)	5000 (4072, 10036)	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, $\times 10^4$/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)	

Treatment			
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%)	
Imaging studies			
Abnormal Chest X-rays results	(n=29)	(n=34)	
Bilateral	19 (70.4%)	8 (23.5%)	
GGO	23 (82.1%)	8 (23.5%)	
Consolidation	11 (40.0%)	2 (5.9%)	
no abnormal shadow	1 (6.7%)	28 (71.8%)	
Abnormal Chest Computed Tomography results	(n=35)	(n=43)	
Bilateral	26 (74.3%)	18 (41.9%)	
GGO	35 (100.0%)	31 (72.1%)	
Consolidation	14 (40.0%)	4 (9.3%)	

Vital signs				
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 (℃)	36.9 (36.5, 37.6)	37.0 (36.5, 37.8)	36.8 (36.5, 37.4)	0.35
SpO_2 (%)	96 (94, 97)	94 (90, 96)	97 (95, 98)	**＜0.001**
MEWS		1 (1, 2)	1 (1, 1)	
qCSI		0 (0, 0.25)	0 (0, 0)	
CURB-65		1 (0, 1)	0 (0, 0)	
ADROP		1 (0, 1)	0 (0, 0)	
qSOFA		0 (0, 1)	0 (0, 0)	
4C mortality score		8 (4, 12)	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.

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			
Valiable	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 (/μL)	1.000	1.000-1.000	0.881
Lym (/μL)	0.999	0.998-1.000	**0.045**
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	**0.007**
BMI	1.201	1.035-1.588	**0.013**
Serum BUN(mg/dL)	1.178	1.005-1.586	**0.018**

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.