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Machine Learning Prediction for Supplemental Oxygen Requirement in Patients with COVID-19

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Background: The coronavirus disease (COVID-19) poses an urgent threat to global public health and is characterized by rapid disease progression even in mild cases. In this study, we investigated whether machine learning can be used to predict which patients will have a deteriorated condition and require oxygenation in asymptomatic or mild cases of COVID-19.

Methods: This single-center, retrospective, observational study included COVID-19 patients admitted to the hospital from February 1, 2020, to May 31, 2020, and who were either asymptomatic or presented with mild symptoms and did not require oxygen support on admission. Data on patient characteristics and vital signs were collected upon admission. We used seven machine learning algorithms, assessed their capability to predict exacerbation, and analyzed important influencing features using the best algorithm.

Results: In total, 210 patients were included in the study. Among them, 43 (19%) required oxygen therapy. Of all the models, the logistic regression model had the highest accuracy and precision. Logistic regression analysis showed that the model had an accuracy of 0.900, precision of 0.893, and recall of 0.605. The most important parameter for predictive capability was SpO_2, followed by age, respiratory rate, and systolic blood pressure.

Conclusion: In this study, we developed a machine learning model that can be used as a triage tool by clinicians to detect high-risk patients and disease progression earlier. Prospective validation studies are needed to verify the application of the tool in clinical practice. (J Nippon Med Sch 2022; 89: 161−168)

Key words: COVID-19, machine learning, oxygen inhalation therapy, pneumonia, SARS-CoV-2

Introduction

Coronavirus disease (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents an urgent threat to global public health. Cases of COVID-19 have several degrees of severity, ranging from asymptomatic to critical condition. Although there is no single definition for severity, approximately 80% of patients with COVID-19 are asymptomatic or have mild disease[1]. Mild disease presentation can generally be defined as the presence of symptoms without any evidence of pneumonia or hypoxia. Home isolation and care can be advised for asymptomatic or mild patients without risk factors, given that measures for appropriate infection prevention and control are observed; pa-

tients should also be closely monitored for any signs or symptoms of deterioration[2]. However, COVID-19 is characterized by rapid disease progression even in mild cases. Shortness of breath has been reported to occur 5-8 days (median) after initial symptom onset[3,4], and 6.5% of patients exhibited rapid disease progression, and 49% of them succumb to the disease[1,5].

The Japanese government has adopted a policy that allows patients with asymptomatic and mild disease who do not require hospitalization to be treated in designated hotels so that their family will not be infected. Patients are then transferred to the hospital in a timely manner when their conditions deteriorate[6]. As of January 23, 2021, Japan has had 356,074 reports of COVID-19 and 4,935 the associated deaths[7]. The third surge occurred, and the number of infected people increased rapidly; this resulted in the deaths of many people with mild illness who were at home or in the designated hotels due to rapid deterioration. It is important to assess patients who are at risk of severe disease and predict their prognosis before they deteriorate for proper intervention execution and appropriate allocation of medical resources.

Various studies have been conducted to predict the prognosis of COVID-19 patients. Most prediction models predicted death, admission to the intensive care unit, ventilator placement, and length of hospital stay; however, only a few studies predicted worsening of the disease with oxygen administration as the outcome[8]. Additionally, because blood examinations and a computed tomography scan cannot be performed in care facilities such as homes or hotels, prognosis must be predicted based only on patient characteristics and vital signs that can be measured by the patients themselves. We investigated whether machine learning can be used to predict which asymptomatic or mild patients with COVID-19 will have a deteriorated condition and require oxygenation.

Materials and Methods

Study Population

This is a retrospective observational study included COVID-19 patients admitted to a single hospital in Tokyo from February 1, 2020, to May 31, 2020, who were either asymptomatic or presented with mild symptoms on admission. Patients with mild diseases were defined as being symptomatic without evidence of viral pneumonia or hypoxia[2], i.e., not requiring supplemental oxygen. According to the WHO guidelines for the diagnosis of COVID-19, nasopharyngeal swab specimens were sub-

jected to real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay to confirm the presence of SARS-CoV-2[2]. Exacerbation was defined as the need for supplemental oxygen during hospitalization. Supplemental oxygen was administered based on the judgment of attending physicians and the treatment guidelines for COVID-19 which was published by the Ministry of Health, Labour and Welfare in Japan. According to this guideline, respiratory failure was defined as an SpO_2 level $\leq$ 93%; this is because the standard definition of respiratory failure, a PaO_2 level $\leq$ 60 mmHg, corresponds to an SpO_2 level $\leq$ 90%, but SpO_2 measurements are expected to have an error of approximately 3%[9]. Approval was obtained by the institutional ethics committee (B-2020-287).

Data Collection

Information was obtained from patients' electronic medical records. Patient characteristics included age, sex, comorbidities, and smoking history (never, past, or current). Risk factors for COVID-19 complications include older age, cardiovascular disease, chronic lung disease, hypertension, diabetes, and obesity[3,10–12]. Cardiovascular disease, respiratory disease, and diabetes were considered as comorbidities, and data were collected. On admission, information regarding vital signs (blood pressure, pulse, respiratory rate, temperature, and SpO_2 on room air) was also collected. Variables were mandatory, and there were no missing values. New variables were created by addition, subtraction, multiplication, and exponential power for body temperature, SpO_2, and respiratory rate.

Statistical Analysis

We used stratified five-fold cross validation to optimize evaluation metrics using seven machine learning algorithms to predict disease progression and analyze important influencing features, namely Decision Tree, K-Nearest Neighbor, Logistic Regression, Naive Bayes, Random Forest, Support Vector Machine, and XGBoost. To tune the parameters of the machine learning, grid search was used for optimization. The grid search was set to maximize recall with a precision of 0.8 or higher. We assessed the predictive performance of our model using the following range of common performance metrics: accuracy, precision (positive predictive value), recall (sensitivity), specificity, F1 score, AUC, and Brier. Python 3.8.3 was used to code the algorithm.

As the respiratory rate may be incorrectly measured by the patients themselves and blood pressure was not measured, we included an analysis excluding respiratory rate that made of only body temperature and SpO_2 using

Table 1　Demographics of patients between exacerbation and non-exacerbation groups

	Total (N=210)	Exacerbation (n=43)	Non-exacerbation (n=167)	P value
Age	55 (39-71)	67 (57-75)	49 (38-69)	<0.001
Sex				0.005
Female	88 (42%)	10 (23%)	78 (47%)	
Male	122 (58%)	33 (77%)	89 (53%)	
Comorbidity				
Cardiovascular	42 (20%)	13 (30%)	29 (17%)	0.06
Respiratory	24 (11%)	7 (16%)	17 (10%)	0.26
Diabetes	11 (5%)	2 (5%)	9 (5%)	0.85
Smoking status				0.14
Never	144 (69%)	25 (58%)	119 (71%)	
Past	30 (14%)	10 (23%)	20 (12%)	
Current	36 (17%)	8 (19%)	28 (17%)	
Body temperature	36.8 (36.5-37.2)	37.2 (36.7-38.5)	36.7 (36.5-37.0)	<0.001
Respiratory rate	18 (16-20)	22 (18-26)	17 (16-20)	<0.001
Systolic blood pressure	126 (114-145)	121 (114-134)	127 (114-147)	0.15
Diastolic blood pressure	80 (72-90)	77 (71-84)	81 (74-90)	0.07
Heart rate	84 (76-93)	88 (80-101)	82 (75-90)	0.004
SpO_2	97 (96-98)	94 (90-97)	98 (97-98)	<0.001

Table 2　Performance comparison of each model

	DT	KNN	LR	NB	RF	SVM	XGB
Accuracy	0.852	0.88	0.9	0.88	0.866	0.89	0.89
Precision	0.81	0.855	0.893	0.777	0.793	0.883	0.828
Recall	0.369	0.513	0.605	0.627	0.488	0.558	0.555
Specificity	0.976	0.976	0.976	0.946	0.963	0.976	0.976
F1 score	0.505	0.606	0.695	0.679	0.583	0.659	0.652
AUC	0.732	0.827	0.875	0.857	0.866	0.892	0.856
Brier	0.125	0.106	0.084	0.114	0.107	0.086	0.12

AUC, area under curve; DT, Decision Tree; KNN, K-Nearest Neighbor; NB, Naive Bayes; LR, Logistic Regression; RF, Random Forest; SVM, Support Vector Machine; XGB, XGBoost.

the model with the highest accuracy.

Continuous variables are shown as median (interquartile range) and analyzed using the Mann-Whitney test. Categorical variables are shown as percentages (%) and analyzed using the chi-square test. Statistical analyses were performed using SPSS software, version 25 (IBM Company, Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

Case Presentation

This study did not include external validation; however, a case presentation was shown to describe the customization of machine learning into clinical practice.

Results

Clinical Characteristics of Patients

A total of 210 patients who were asymptomatic or had mild COVID-19 were included in the study. Median patient age was 55 (39-71) years, with 129 (58%) male and 88 (42%) female patients. Patient history features included 42 (20%) patients with cardiovascular disease, 24 (11%) with respiratory disease, and 11 (5%) with diabetes. Among these patients, 43 (20%) required oxygen therapy. Age, sex, cardiovascular disease, temperature, respiratory rate, heart rate, and SpO_2 were the parameters observed in both the exacerbation group (comprising patients who required supplemental oxygen during hospitalization) and the non-exacerbation group (**Table 1**).

Machine Learning

Of all the models, logistic regression had the highest accuracy and precision (**Table 2**). Logistic regression analysis had an accuracy of 0.900, precision (positive predictive value) of 0.893, and recall (sensitivity) of 0.605.
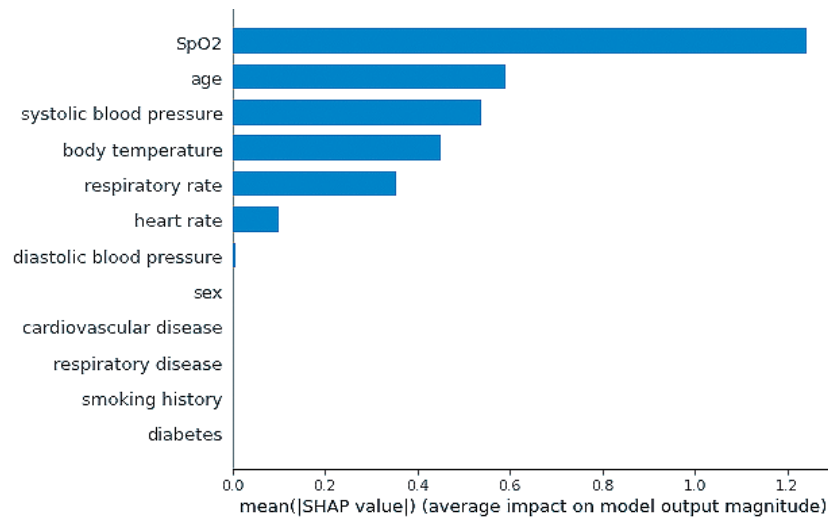
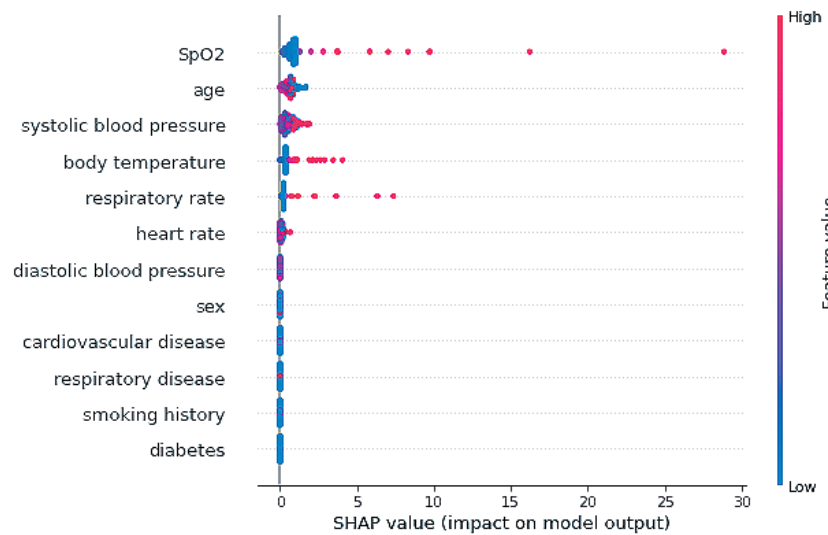Fig. 1 Feature importance ranking of logistic regression

Fig. 2 Overall analysis of features (SHAP value)
This figure shows the influence of each feature on the objective variable; if the SHAP value is positive, it has a positive influence on the objective variable. The color of each element indicates the value of the features: the redder the color, the higher the value. However, for SpO_2, the large-small relationship is reversed in the process of feature engineering.
SHAP, SHapley Additive exPlanations

Therefore, logistic regression was used to analyze the parameters. The most important predictive parameter was SpO_2, followed by age, respiratory rate, and systolic blood pressure (**Fig. 1**). **Figure 2** shows the SHapley Additive exPlanations (SHAP), which represent the contribution of each parameter to the prediction results of the model. If the SHAP value is positive and red, there could be a positive correlation. **Figure 3** shows the correlation matrix, which represents the correlation coefficient between parameters (the darker the color, the stronger the correlation).

When respiratory rate was excluded from the analysis, precision decreased from 0.893 to 0.843. When we used only body temperature and SpO_2, precision decreased from 0.893 to 0.850 (**Table 3**).

Case Presentation

An 80-year-old woman who presented with fever and cough. She had a history of diabetes mellitus and cardiovascular disease, and was a current smoker. Three days after the onset of symptoms, she was transferred to the hospital because of exacerbation of symptoms. A PCR test was performed on a nasopharyngeal specimen, and
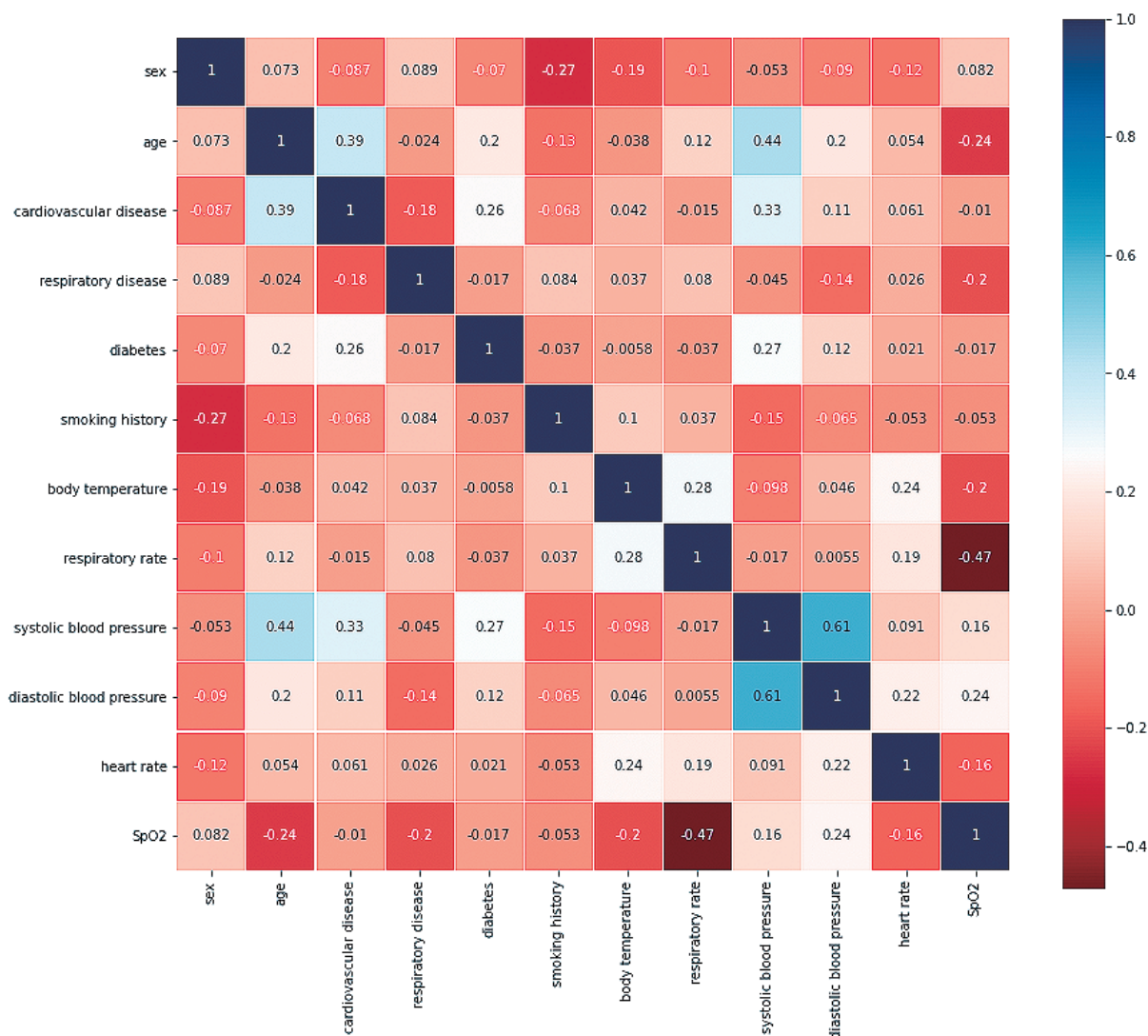
Correlation of Features

Fig. 3 Correlation matrix
The correlation coefficient (the Pearson product-moment correlation coefficient) between the two features is shown (the darker the color, the stronger the correlation). SpO₂, the most important parameter, is correlated with respiratory rate, age, systolic blood pressure, respiratory diseases, and body temperature. Age is correlated with systolic blood pressure, heart disease, SpO₂, diabetes, and diastolic blood pressure.

Table 3 Performance comparison of each feature used

	All	All except RR	BT and SpO₂
Accuracy	0.900	0.900	0.895
Precision	0.893	0.843	0.850
Sensitivity (Recall)	0.605	0.630	0.580
Specificity	0.976	0.970	0.976
F1 score	0.695	0.700	0.677
AUC	0.875	0.863	0.869
Brier	0.084	0.088	0.090

AUC, area under curve; BT, body temperature; RR, respiratory rate; SpO₂, peripheral oxygen saturation

it was positive for SARS-CoV-2. On the day of admission, her blood pressure was 164/78 mmHg, pulse was 100/min, respiratory rate was 18/min, body temperature was 38.8°C, SpO₂ was 96% on room air, and the probability of supplementary oxygen requirement was 37%. Favipiravir (brand name, Avigan) was administered orally. The next day, her blood pressure was 140/72 mmHg, pulse was 88/min, respiratory rate was 18/min, temperature was 39.8°C, and SpO₂ was 96% on room air. Although SpO₂ was unchanged, the probability of supplementary oxygen requirement increased to 95%. On the same day, her SpO₂ dropped, requiring supplemental oxygen. Thereafter, she gradually deteriorated and was

intubated on the sixth day after admission.

Discussion

Using machine learning, we predicted the requirement for supplemental oxygen in asymptomatic patients or those with mild COVID-19 based only on vital signs that could be measured by the patients themselves.

Peripheral arterial oxygen saturation (SpO_2) was of the highest importance in this model, and was measured as a surrogate marker for tissue oxygenation. It is the standard for continuous, noninvasive assessment of oxygenation.[13] In fact, home pulse oximetry monitoring could identify the need for hospitalization in initially mild COVID-19 patients and reduce unnecessary emergency department revisits[14-16]. In our case, deterioration could be predicted even when SpO_2 was 96% and supplemental oxygen was not necessary because of the comprehensive evaluation using not only SpO_2 but also other features.

In previous studies, risk factors included older age more than 60 years (increasing with age), diabetes, hypertension, cardiovascular disease, chronic lung disease cerebrovascular disease, chronic kidney disease, immunosuppression, smoking, and obesity[2,3,10-12]. In the present study, age was also of high importance; however, comorbidities (cardiovascular disease, respiratory disease, and diabetes) were not. These features were relatively highly correlated with SpO_2, age, and systolic blood pressure (all of which are of high importance) and may have resulted in their low importance in the present model.

There are several strengths to this study. First, it does not require blood tests or imaging studies. Previous studies have reported important prognostic factors such as comorbidities, age, sex, lymphocyte count, C-reactive protein, body temperature, creatinine, and imaging findings[8]. However, it is logistically difficult to perform daily blood tests in patients with asymptomatic or mild COVID-19 because they stay at home or in hotels. This study suggested that vital signs alone can predict exacerbations with high accuracy. Second, physical contact between healthcare workers and patients should be significantly reduced during the pandemic period; this, in turn, minimizes the risk of infection. There have been cases in which healthcare workers have died due to infection from patients, which is a serious problem[17]. Even in the absence of infection, the mental health of healthcare workers treating and caring for COVID-19 patients can be greatly affected[18,19]. Therefore, being able to predict prognosis only using values that can be measured by the patients themselves is a great advantage. Third, we can objectively determine disease severity by changing the probability of supplemental oxygen requirement. Asymptomatic or mild patients exhibit only small changes in vital signs; therefore, subjective evaluation of symptoms is required in many algorithms[20,21]. This model is expected to be used for decision making, such as the need for admission, because it can objectively and numerically show the trend of exacerbation probability (values from 0 to 100). This prediction model recommends admission to the hospital when the probability is greater than 50%. Fourth, the exacerbation probability in multiple patients can be objectively compared. Scoring for patients with pneumonia (using CURB-65, A-DROP, Pneumonia Severity Index, SMART-COP, NEWS2, CRB-65, or qSOFA) can also predict the severity of COVID-19 with high accuracy[22-24]. In addition, a new scoring system for COVID-19 has been proposed[25-28]. However, it is difficult to compare the probabilities of exacerbation between patients when they have the same score using the scoring system (usually due to similarities in their vital sign values). It is expected to be used as a triage tool because it allows an objective comparison of the exacerbation probabilities.

This study has several limitations. First, it was a retrospective observational retrospective study with a small sample size from a single institution. Prospective validation studies are needed in clinical practice. However, using new patients in the supplemental material, we were able to predict worsening of respiratory condition without changes in respiratory status. Second, recall is low at the cost of maximizing precision. We maximized precision to minimize the burden on hospitals and to select only those who were most likely to deteriorate. However, once a patient is diagnosed with COVID-19, vital signs and physical condition are checked daily, and the decision to hospitalize is not based on a single vital sign. It is possible to predict deterioration from the trends of multiple measurements even if the recalls are low. Third, it is assumed that vital signs and SpO_2 were measured with the same quality as that of medical personnel in the hospital. Excluding the respiratory rate from the features or using only vital signs of body temperature and SpO_2 reduces accuracy, and thus, it is desirable to measure the respiratory rate; however, it is necessary to impute the missing values when it cannot be measured. Some of the home-based devices used to measure vital signs are not as accurate as medical devices. For example, smartphone-based pulse oximetry is insufficient to recommend for hypoxic patients.[29] Fourth, selection bias may have occurred. Although this study included hospitalized pa-

tients with mild illnesses, it is possible that patients who were likely to require oxygen therapy were selected.

Conclusions

In this study, we developed a machine learning model with 90% prediction accuracy that can be used as a triage tool by clinicians to detect high-risk patients and disease progression earlier.

Authors' contributions: YI, NM, KN and KO contributed to the design and implementation of the research. NM, TM, KS, HO, and YT collected data. KN and KO performed machine learning and analyzed the data. YI, KN, KO, NM, TT and SY contributed to the interpretation of the results. YI wrote the original draft of the manuscript. TT, MS, HO and SY critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript to be published.

Conflict of Interest: The authors declare that they have no competing interests.

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