# Predictive Factors for Tracheal Intubation in Patients with Coronavirus Disease 2019 Treated Using a High-flow Nasal Cannula

Yuichi IKUYAMA[1)*], Atsuhito USHIKI[1)], Jumpei AKAHANE[1)], Yoshitaka YAMAZAKI[2)]
Masanobu KIMOTO[2)], Takashi ICHIYAMA[1)], Yosuke WADA[1)] and Masayuki HANAOKA[1)]

1) *First Department of Internal Medicine, Shinshu University School of Medicine*
2) *Center of Infectious Diseases, Nagano Prefectural Shinshu Medical Center*

**Background** : In Japan, patients with coronavirus disease 2019 (COVID-19)* requiring a high-flow nasal cannula (HFNC) are often initially treated in non-specialized facilities and transferred to an intensive care unit if tracheal intubation is required. We aimed to investigate the factors associated with severe respiratory failure requiring tracheal intubation at an early stage in patients with COVID-19 treated using HFNCs.

**Methods** : This retrospective cohort study compared the clinical features of consecutively enrolled patients with polymerase chain reaction-confirmed severe acute respiratory syndrome coronavirus-2 infection admitted to two centers in Japan between early February 2020 and late June 2021.

**Results** : A total of 35 patients with COVID-19 treated using HFNCs were included. Treatment success and failure occurred in 25 and 10 patients, respectively. The oxygen saturation (ROX) index (ratio of oxygen saturation [$SpO_2$] to fraction of inspired oxygen [$FiO_2$] and the respiratory rate) 12 h post-HFNC insertion was a useful predictor of HFNC failure (success group, 8.0 ; failure group, 6.5 : $P = 0.0005$). Moreover, the time from symptom onset to respiratory failure was significantly shorter in the failure group than in the success group (3.0 and 5.0 days, $P = 0.004$).

**Conclusions** The ROX index and time from symptom onset to respiratory failure were useful predictors of HFNC failure. *Shinshu Med J 71 : 403—409, 2023*

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**Key words** : high-flow nasal cannula, COVID-19, ROX index, tracheal intubation, oxygen therapy

**Abbreviations** : COVID-19, coronavirus disease 2019 ; HFNC, high-flow nasal cannula ; $SpO_2$, oxygen saturation ; $FiO_2$, fraction of inspired oxygen ; IPPV, invasive positive pressure ventilation ; ICU, intensive care unit ; ROX, ratio of oxygen saturation ; AUC, area under the curve

## I Introduction

A high-flow nasal cannula (HFNC) can maintain a high inhaled oxygen concentration by administering warmed and humidified oxygen to the patient at a high flow rate. By reducing the number of patients who require invasive positive-pressure ventilation (IPPV), HFNC use minimizes the risk of ventilator-associated pneumonia. In addition, HFNC use improves the 90-day mortality rate and the number of ventilator-free days at 28 days compared with standard oxygen therapy or noninvasive ventilation[1)]. Moreover, admission to the intensive care unit (ICU) is not always necessary, and medical resources can be conserved. Therefore, in Japan, patients with COVID-19 requiring HFNCs are often initially treated in non-specialized facilities without an ICU and are transferred to a facility with an ICU if IPPV is required.

* Corresponding author : Yuichi Ikuyama
First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : ikuyama@shinshu-u.ac.jp

In patients with coronavirus disease 2019 (COVID-19), HFNC use reduced the need for mechanical ventilation and improved oxygenation compared with that with standard oxygen therapy[2]. Further, in patients with COVID 19-related acute respiratory failure, HFNC use increased in the number of ventilator-free days compared with that with early IPPV initiation[3]. Moreover, a previous report showed that the HFNC application reduced the mortality rate in patients with COVID-19 compared with that with IPPV[4], and in another study, delayed tracheal intubation was associated with poor clinical outcomes[5]. Therefore, if HFNC treatment fails to improve gas exchange and ventilatory function, tracheal intubation should be performed at the earliest.

The wave of severe acute respiratory coronavirus-2 (SARS CoV-2) infection in Japan was substantially large, and intensive medical care resources were severely limited. Therefore, it was important to identify cases with poor therapeutic effects of HFNC at an early stage and conserve medical resources.

In previous studies, the ratio of the oxygen saturation (ROX) index at 6 h, 12 h, and 72 h was used as a simple, non-invasive, and promising tool for predicting HFNC discontinuation : it could be used for the assessment of progress and risk of intubation in patients with COVID-19 presenting with pneumonia[6)-9)]. The ROX index refers to the combination of the ratio of oxygen saturation ($SpO_2$) to the fraction of inspired oxygen ($FiO_2$) and the respiratory rate. Although useful, it requires some time for calculation. Moreover, the ROX index can be calculated after introducing HFNC. Therefore, a simple indicator for tracheal intubation is required. Accordingly, this study aimed to identify suitable indicators that can predict tracheal intubation earlier than the ROX index in patients with severe respiratory failure.

## Ⅱ Materials and Methods

We retrospectively reviewed the medical records of patients with COVID-19 who received conventional oxygen therapy through HFNCs at the Shinshu University Hospital (Matsumoto, Japan) and Nagano Prefectural Shinshu Medical Center (Suzaka, Japan). We included consecutive patients with polymerase chain reaction-confirmed SARS CoV-2 infection who were admitted to these hospitals between early February 2020 and late June 2021. Patients who required HFNCs after extubation were excluded from the study.

We classified patients who received HFNC therapy because of deterioration as HFNC success or failure, depending on whether intubation could be avoided. Patients who died without being intubated because of do-not-intubate orders were classified as cases of HFNC failure. The ROX index was defined as the ratio of $SpO_2$ to $FiO_2$ (%) and the respiratory rate (breaths/min). The median number of days from HFNC application to tracheal intubation was 1 day (range, 0.5-2.5 days) in the failure group. Because data at 6 h after HFNC introduction were missing, we investigated the ROX index at 12 h in this study.

This study was performed in accordance with the Declaration of Helsinki and was approved by our Institutional Review Board (approval number 5228, July 15th, 2021). The requirement for written informed consent was waived because of the use of de-identified data collected retrospectively. Furthermore, this research used an opt-out consent model, which meant that patients could opt out at any time and have their information deleted from the registry.

HFNC use raises concerns regarding the increased risk of viral transmission due to aerosol dispersion[10)11)]. In this study, staff providing COVID-19 medical care services underwent training for personal protective equipment donning and doffing. The medical care staff donned personal protective equipment, including long-sleeved gowns, gloves, N95 masks, surgical masks with face shields, and hair caps, while attending to patients receiving HFNC or conventional oxygen therapy. Nosocomial infections in healthcare workers were not reported during the study period.

### A Data analysis

Continuous data are presented as median (interquartile range [IQR], 25th quartile, 75th quartile). The t-test and Mann-Whitney U-test were used to compare continuous data with normal and non-normal distributions, respectively. Categorical variables were compared using the chi-square test or Fisher's exact

Table 1　Demographic and clinical characteristics of the patient groups

| Characteristic | All patients (n = 35) | HFNC success (n = 25) | HFNC failure (n = 10) | *P*-value (HFNC success vs. HFNC failure) |
|---|---|---|---|---|
| Age, median (IQR) years | 67.0 (58.0, 82.0) | 66.0 (57.5, 76.0) | 67.0 (62.0, 82.0) | 0.22 |
| ≥ 65, n (%) | 21 (60 %) | 13 (52 %) | 8 (80 %) | 0.13 |
| Number of comorbidities, n (IQR) | 1.6 (1, 2) | 2 (1, 2) | 2 (1, 2) | 0.37 |
| Heart disease | 4 (11 %) | 4 (16 %) | 0 (0 %) | 0.30 |
| Cerebrovascular disease | 3 (9 %) | 3 (12 %) | 0 (0 %) | 0.54 |
| Hypertension | 17 (49 %) | 14 (56 %) | 3 (30 %) | 0.26 |
| Diabetes mellitus | 15 (43 %) | 11 (44 %) | 4 (40 %) | 1.0 |
| Kidney disease | 3 (9 %) | 2 (8 %) | 1 (10 %) | 1.0 |
| Respiratory disease | 7 (20 %) | 4 (16 %) | 3 (30 %) | 0.38 |
| Malignant tumor under treatment | 3 (9 %) | 2 (8 %) | 1 (10 %) | 1.0 |
| BMI, median (IQR) kg/m$^2$ | 26.5 (23.2, 30.5) | 28.1 (24.5, 30.8) | 24.2 (23.8, 28.2) | 0.15 |
| Sex, male, n (%) | 23 (67.7 %) | 15 (71.4 %) | 6 (60.0 %) | 0.82 |
| Brinkman index, median (IQR) | 200 (0, 600) | 20 (0, 550) | 470 (85, 1050) | 0.70 |
| $SpO_2$ on room air, median (IQR) % | 91.5 (88.3, 94.0) | 92.0 (87.5, 94.5) | 91.5 (87.3, 93.5) | 0.36 |
| Patients treated with methylprednisolone pulse therapy (500-1000 mg/day three times per week) | 9 (26 %) | 6 (24 %) | 3 (30 %) | 0.13 |
| Initial steroid dose※ | 44 (40-88) | 44 (40-88) | 50 (45.5-87.5) | 0.31 |
| Antiviral drugs | | | | |
| Remdesivir | 28 (80 %) | 20 (80 %) | 8 (80 %) | 0.22 |
| Favipiravir | 4 (11 %) | 2 (8 %) | 2 (20 %) | 0.18 |
| Lopinavir and Ritonavir | 3 (9 %) | 3 (12 %) | 0 | − |

HFNC, high-flow nasal canula ; IQR, interquartile range ; BMI, body mass index.
※ In case patients who received steroid pulse therapy, dose after steroid pulse therapy.

test, as appropriate (expected value＜0.05 in one cell).

The ability of each risk score and biomarker to discriminate between patients with HFNC success and HFNC failure was evaluated by calculating the area under the curve (AUC) of the receiver operating characteristic and its 95 % confidence interval. The optimal cutoff values to assess HFNC failure were evaluated using Youden's index. Statistical analysis was performed using Windows-compatible software (StatFlex version 7 : Artech Co. Ltd., Osaka, Japan). Statistical significance was set at $P < 0.05$.

## Ⅲ　Results

### A　Baseline characteristics

Among the patients with COVID-19 treated during the study period, 35 patients met the inclusion criteria. The median age was 67.0 (IQR, 58.0, 82.0) years, and 21 (67.7 %) patients were men. The baseline characteristics of the patients are listed in **Table 1**. All patients in this study received corticosteroids and antivirals, and none were vaccinated. The frequency of steroid pulse and initial corticosteroid dose was not significantly different between the HNFC success and failure groups (in case patients who received steroid pulse therapy, describe the dose after steroid pulse therapy)n.

### B　Comparison of clinical data between the HFNC success and failure groups

The HFNC success and failure groups included 25 and 10 patients, respectively. There were no significant differences in age, sex, body mass index, or the number of complications, which are risk factors for severe COVID-19[12)-14)], between the HFNC success and failure groups. Further, the laboratory test results were not significantly different between the two groups **(Table 2)**. The median period from symptom onset to respiratory failure was significantly shorter in the HFNC failure group than in the HFNC success

Table 2　Laboratory findings at admission

| | All patients (n = 35) | HFNC success (n = 25) | HFNC failure (n = 10) | *P*-value (HFNC success vs. HFNC failure) |
|---|---|---|---|---|
| WBC, /μL | 4600 (3200, 6900) | 5150 (3697, 7125) | 4885 (3055, 7720) | 0.76 |
| Lym, /μL | 1100 (875, 1338) | 1000 (800, 1100) | 1210 (1159, 1458) | 0.29 |
| LDH, IU/L | 325 (265, 458) | 358 (298, 456) | 287 (215, 535) | 0.96 |
| BUN, mg/dL | 13.7 (12.8, 16.9) | 14.1 (12.8, 16.9) | 13.6 (13.0, 16.9) | 0.61 |
| Cre, mg/dL | 0.89 (0.74, 1.03) | 0.94 (0.74, 1.07) | 0.85 (0.61, 0.91) | 0.07 |
| BUN/Cre, mg/dL | 17.4 (13.0, 19.6) | 17.3 (13.9, 18.2) | 18.9 (14.2, 21.3) | 0.22 |
| CRP, mg/dL | 5.0 (2.3, 11.9) | 5.7 (2.4, 12.1) | 7.1 (1.8, 11.8) | 0.71 |
| KL-6, U/L | 386 (247, 484) (n = 13) | 328 (247, 440) (n = 9) | 457 (344, 548) (n = 4) | 0.46 |
| Ferritin, μg/L | 630 (291, 921) (n = 17) | 642 (330, 921) (n = 13) | 507 (507, 782) (n = 4) | 0.86 |
| D-dimer, μg/mL | 1.0 (0.5, 1.7) | 0.9 (0.5, 1.6) | 1.1 (1.0, 4.6) | 0.42 |

All values are presented as median (interquartile range).
HFNC, high-flow nasal canula ; WBC, white blood cell count ; Lym, lymphocyte count ; LDH, lactate dehydrogenase ; BUN, blood urea nitrogen ; Cre, creatinine ; CRP, C-reactive protein ; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6.

Table 3　Comparison of the clinical courses and outcomes between the HFNC success and failure groups

| Variable | All patients (n = 35) | HFNC success (n = 25) | HFNC failure (n = 10) | *P*-value (HFNC success vs. HFNC failure) |
|---|---|---|---|---|
| Duration between diagnosis and respiratory failure, median (IQR) days | 2.0 (0.0, 3.0) | 2.0 (0.0, 3.5) | 2.5 (0.8, 3.5) | 0.87 |
| Number of days from diagnosis to HFNC initiation, median (IQR) | 5.0 (1.0, 7.0) | 5.0 (2.0, 7.0) | 5.0 (1.0, 7.5) | 0.59 |
| Duration between respiratory failure and HFNC application, median (IQR) days | 2.0 (1.0, 4.75) | 2.0 (1.0, 4.5) | 1.0 (0.5, 4.0) | 0.68 |
| Duration between symptom onset and respiratory failure, median (IQR) days | 4.0 (3.0, 6.0) | 5.0 (4.0, 6.5) | 3.0 (3.0, 4.5) | 0.044 |
| Intubation, n (%) | 7 (20 %) | 0 (0 %) | 7 (70 %) | |
| Death, n (%) | 3 (8.6 %) | 0 (0 %) | 3 (30 %) | |

HFNC, high-flow nasal canula ; IQR, interquartile range.

group **(Table 3)**. Three patients in the HFNC failure group died.

**C　Comparison of the ROX index between the HFNC success and failure groups**

The duration of HFNC use was significantly longer in the HFNC success group than in the failure group (8.0 [IQR, 7.0, 11.0] and 2.0 [IQR, 0.8, 3.0] days, respectively) **(Table 4)**. The ROX index at 12 h was significantly higher in the HFNC success group than in the HFNC failure group (8.0 [IQR, 7.5, 8.9] and 6.5 [IQR, 5.8, 7.3], respectively) **(Table 4)**.

**D　Receiver operating characteristic analysis and comparison of predictive ability for HFNC failure**

**Fig. 1** shows the AUC according to the ROX index at 12 h, and median duration from symptom onset to respiratory failure. The AUCs (± standard error) of the ROX index at 12 h and duration between symptom onset and respiratory failure were 0.91 (± 0.05) and 0.73 (± 0.09), respectively. The optimal cutoff values to assess HFNC failure using Youden's index were 7.0 and 3.5 days for the ROX index at 12 h and time between symptom onset and respiratory failure, re-

Table 4　Clinical parameters after HFNC initiation

| Parameter | All patients (n = 35) | HFNC success (n = 25) | HFNC failure (n = 10) | *P*-value (HFNC success vs. HFNC failure) |
|---|---|---|---|---|
| HFNC duration, days | 7.0 (3.0, 10.0) | 8.0 (7.0, 11.0) | 2.0 (0.8, 3.0) | 0.004 |
| Maximum $FiO_2$ | 0.60 (0.53, 0,73) | 0.60 (0.50, 0.60) | 0.80 (0.65, 0.80) | 0.004 |
| O2 Flow, L/min | 40 (40, 50) | 40 (40, 50) | 40 (29, 40) | 0.59 |
| ROX index at 12 h | 8.0 (6.8, 9.0) | 8.0 (7.5, 8.9) | 6.5 (5.8, 7.3) | 0.0005 |

All values are presented as median (interquartile range).
HFNC, high-flow nasal cannula : ROX, ratio of oxygen saturation

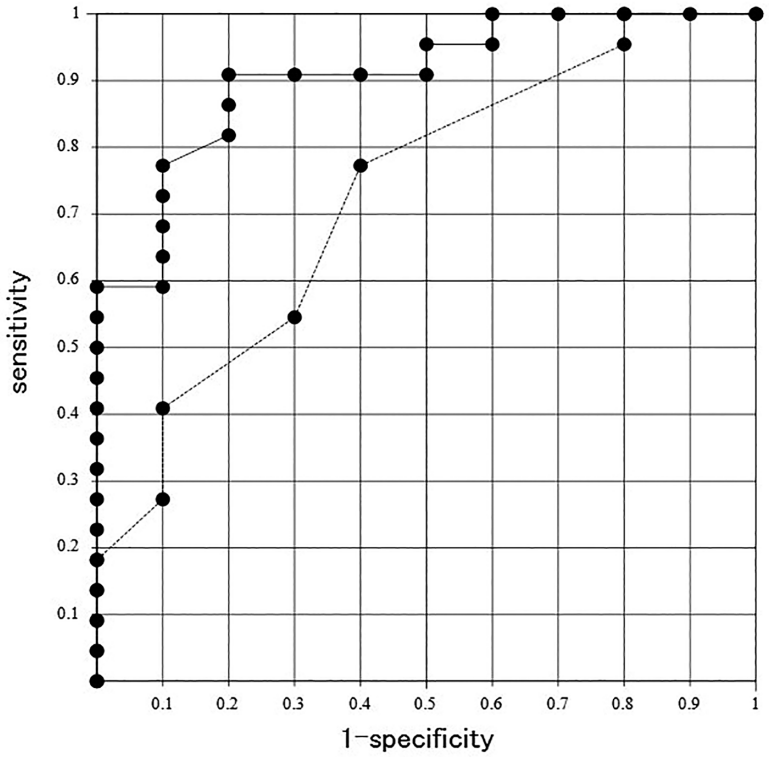


Fig. 1　Receiver operating characteristic curves for the ratio of oxygen saturation (ROX) index (12 h) (solid line) and median time from symptom onset to respiratory failure in patients with coronavirus disease 2019 (dotted line)

spectively.

## Ⅳ　Discussion

In this study, tracheal intubation was avoided in 25 out of 35 patients (71.4 %). This result was better than that reported previously (8 out of 15 patients, 53.3 %) in Japan[15] and may be related to the advances in treatment, such as the use of corticosteroids and antiviral drugs.

In a previous study, the ROX index at 12 h was a useful predictor of HFNC failure in patients with COVID-19 who received HFNCs[6]. Similar results were obtained in this study.

The present study revealed that the period from symptom onset to respiratory failure was significantly shorter in the HFNC failure group than in the HFNC success group (3.0 [IQR, 3.0, 4.5] and 5.0 [IQR, 4.0, 6.5] days, respectively). This suggests that among patients with HFNCs, tracheal intubation is more likely to be required in those exhibiting a shorter period from

symptom onset to respiratory failure. To the best of our knowledge, this association has not been reported previously. This allows for predicting the outcome at HFNC initiation and is highly valuable in clinical practice.

The ROX index can be calculated after HFNC application. In contrast, the median time from symptom onset to respiratory failure can be evaluated earlier. Although the AUC of the receiver operating characteristic for the median time from symptom onset to respiratory failure was smaller than that for the ROX index, it is known before HFNC application. Therefore, the median time from symptom onset to respiratory failure is an important indicator that can help conserve medical resources and ensure cooperation between hospitals.

In patients exhibiting a shorter period between symptom onset and respiratory failure, oxygen saturation should be monitored more carefully and IPPV should be initiated if the respiratory condition worsens. Furthermore, it may be necessary to consider the possibility of ventilator management in patients with rapid respiratory failure.

Despite these novel findings, this study had some limitations. First, this was a retrospective study conducted at two facilities, possibly resulting in selection bias, and the severity may have been different between facilities. Second, in many cases, tracheal intubation was considered when the $FiO_2$ was consistently $\geq 0.6$ : however, a well-defined protocol for HFNC initiation was lacking. Thus, the treatment results could have varied depending on the judgment of individual physicians. Third, the ROX index at 6 h is more useful than that at 12 h in patients with COVID-19 with hypoxemia[9]. However, in this study, some data on the ROX index at 6 h were missing : therefore, it was not used. Fourth, this study could not examine COVID-19 variants. This study was conducted between February 2020 and June 2021. This is the period from the first confirmation of COVID-19 to the fourth wave in Japan. B.1.1.7 was prevalent in the fourth wave in Japan[16]. Thus, differences results may be obtained in patients infected with the current variants of SARS CoV-2.

## V Conclusions

Delay in tracheal intubation may increase the risk of mortality, and it is important to use the ROX index and time from symptom onset to respiratory failure simultaneously to ensure that patients requiring transition from HFNC to tracheal intubation are not missed. The time from symptom onset to respiratory failure, which can be determined upon admission, has a predictive value comparable with that of the ROX index.

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## Conflict of interest

The authors declare no conflicts of interest.

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