

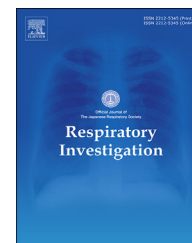


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Original article

High-flow nasal cannula oxygen therapy in hypoxic patients with COVID-19 pneumonia: A retrospective cohort study confirming the utility of respiratory rate index



Yuichiro Takeshita ^a, Jiro Terada ^{a,b,*}, Yasutaka Hirasawa ^a,
Taku Kinoshita ^a, Hiroshi Tajima ^a, Ken Koshikawa ^{a,b}, Toru Kinouchi ^{a,b},
Yuri Isaka ^{a,b}, Yu Shionoya ^a, Yuji Tada ^a, Kenji Tsushima ^a

^a Department of Pulmonary Medicine, International University of Health and Welfare Narita Hospital, 852 Hatakeda, Narita, Chiba 286-8520, Japan

^b Department of Respiriology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, 260-8670, Japan

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ABSTRACT

Background: Although high-flow nasal cannula (HFNC) oxygen treatment has been frequently used in coronavirus disease 2019 (COVID-19) patients with acute respiratory failure after the 3rd wave of the pandemic in Japan, the usefulness of the indicators of ventilator avoidance, including respiratory rate-oxygenation (ROX) index and other parameters, namely oxygen saturation/fraction of inspired oxygen ratio and respiratory rate (RR), remain unclear.

Methods: Between January and May 2021, our institution treated 189 COVID-19 patients with respiratory failure requiring oxygen, among which 39 patients requiring HFNC treatment were retrospectively analyzed. The group that switched from HFNC treatment to conventional oxygen therapy (COT) was defined as the HFNC success group, and the group that switched from HFNC treatment to a ventilator was defined as the HFNC failure group. We followed the patients' oxygenation parameters for a maximum of 30 days.

Results: HFNC treatment success occurred in 24 of 39 patients (62%) treated with HFNC therapy. Compared with the HFNC failure group, the HFNC success group had a significantly higher degree of RR improvement in the univariate analysis. Logistic regression analysis of HFNC treatment success adjusting for age, respiratory improvement, and a ROX index ≥ 5.55 demonstrated that an improved RR was associated with HFNC treatment success. The total COT duration was significantly shorter in the HFNC success group than in the HFNC failure group.

Abbreviations: ARF, acute respiratory failure; BMI, body mass index; COT, conventional oxygen therapy; COVID-19, coronavirus disease 2019; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; ROX, respiratory rate-oxygenation; RR, respiratory rate; SD, standard deviation; SPO₂, oxygen saturation.

* Corresponding author. Department of Pulmonary Medicine, International University of Health and Welfare Narita Hospital, 852 Hatakeda, Narita, Chiba 286-8520, Japan.

E-mail address: jirotera@iuhw.ac.jp (J. Terada).

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Conclusions: HFNC treatment can be useful for ventilator avoidance and allow the quick withdrawal of oxygen administration. RR improvement may be a convenient, useful, and simple indicator of HFNC treatment success.

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1. Introduction

The coronavirus disease 2019 (COVID-19) global pandemic is widespread, and the number of deaths is increasing. Thus, preventing the deterioration of patients with COVID-19 is crucial. The near-collapse of the healthcare systems in certain cities worldwide has led to the use of the high-flow nasal cannula (HFNC) oxygen treatment, which has the potential to reduce the need for intubation and the number of ventilators required [1]. The relatively positive opinions regarding the efficacy of the HFNC treatment for respiratory failure caused by COVID-19 have been obtained from several clinical and academic societies, such as the Society of Critical Care Medicine and the European Society of Intensive Medicine [2], the National Institutes of Health [3], and the Australian and New Zealand Intensive Care Society [4].

HFNC treatment had not been widely used in Japan for respiratory failure caused by COVID-19 pneumonia because intubation was preferentially considered for such patients at the beginning of the pandemic, particularly in the 1st and 2nd pandemic waves in 2020, because of anxiety over the risk of aerosol dispersion that may infect the healthcare providers. At present, the HFNC treatment is conditionally possible if a patient is managed in a negative-pressure private room or in the red zone and uses a surgical mask and if the medical practitioner has appropriate infection control with full personal protective equipment [5]. Under these conditions, a recent online questionnaire survey by the Japanese Respiratory Society revealed that the use of HFNC treatment in COVID-19 cases in Japan had increased, partly due to the limited availability of medical resources during the larger 3rd wave coupled with increased internal reports on the success of the HFNC treatment [6,7].

Although the HFNC treatment is expected to have the potential to avoid intubation in patients with acute respiratory failure (ARF) caused by COVID-19 pneumonia, delaying the intubation timing may worsen the patient's prognosis, possibly leading to the development of lung injury due to continued spontaneous breathing with atelectasis [8]. Thus, an index for the early prediction of whether HFNC treatment can help to avoid ventilator use is essential in this clinical setting. First reported by Roca et al., the respiratory rate-oxygenation (ROX) index, defined as the ratio of oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2) to the respiratory rate (RR), has been used to assess the need for intubation in patients with pneumonia and hypoxemic respiratory failure [9]. However, the ROX index cutoff value in patients with COVID-19 pneumonia varies across studies. Hu et al. reported that a ROX index of >5.55 at 6 h after HFNC

treatment initiation had a good predictive capacity for the HFNC treatment outcomes [10]. Another study demonstrated that a ROX index of >3.0 at 2, 6, and 12 h after HFNC treatment initiation showed 85.3% sensitivity for identifying the subsequent HFNC treatment success [11]. Thus, while the ROX index seems useful in assessing the risk for intubation in patients with hypoxic COVID-19 pneumonia, the utility of the ROX index cutoff value and the timing for HFNC remains unclear.

This study retrospectively analyzed a total of 39 consecutive COVID-19 patients with ARF, who were treated with HFNC therapy to confirm the success rate of the HFNC treatment and the usefulness of indicators of ventilator avoidance, including the ROX index or other parameters, such as the SpO_2/FiO_2 ratio and RR.

2. Patients and methods

2.1. Ethical approval

All the study procedures were conducted according to the standards of the Ethical Review Board of the International University of Health and Welfare (approval number 20-Nr-101; 2021/02/22 approved) and conformed to the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The requirement for informed consent was waived by the Ethics Committee because this retrospective analysis was limited to preexisting data collected as part of the standard of care by respiratory physicians. Furthermore, data anonymization and privacy issues were protected.

2.2. Study design and subjects

This single-center retrospective study was conducted on consecutive adult patients with COVID-19, who were admitted to the International University of Health and Welfare Narita Hospital between January and May 2021. Infection was confirmed using quantitative reverse-transcription polymerase chain reaction assays. Among 385 consecutive patients with pneumonia admitted to the pulmonology unit in this period, 189 patients presented with respiratory failure requiring oxygen administration. Of these, 134 patients were treated only with conventional oxygen therapy (COT) requiring oxygen supplementation of ≤ 4 L/min, 6 patients were treated with ventilator support after COT, including 5 patients treated with invasive positive-pressure ventilation and 1 patient treated with noninvasive positive-pressure ventilation, and 49 patients requiring oxygen supplementation of ≥ 5 L/min were treated with HFNC therapy. After

excluding 10 patients due to do-not-intubate orders or insufficient data, the final study cohort comprised 39 consecutive patients (Fig. 1).

2.3. Respiratory device and monitor

The Airvo 2 Nasal High-Flow System (Fisher & Paykel Healthcare) was used to deliver the HFNC treatment. The HFNC treatment was initiated at a temperature of 31°C–37°C, with high-flow oxygen of 40 L/min according to the tolerance; additionally, FiO_2 was adjusted to maintain the $\text{SpO}_2 > 94\%$. All the patients receiving HFNC treatment were fitted with a noninvasive measurement device for electrocardiogram (ECG), RR, and SpO_2 monitoring. We placed cameras to film videos of all the patients with HFNCs to observe the respiratory status. All patients with HFNCs were instructed to wear a surgical mask over the nasal cannula to prevent aerosol transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). If the flow was tolerated, it was increased by 5 L/min to a maximum of 60 L/min. Based on the target SpO_2 value and the respiratory status, the FiO_2 was adjusted by 5%–10%. When FiO_2 could be adjusted to $\leq 40\%$, the treatment was switched to conventional oxygen therapy (COT), indicating HFNC treatment success. Ventilator support was administered in patients who exhibited the following conditions: (1) no respiratory improvement despite an HFNC setting of ≥ 50 L/min and an FiO_2 of $\geq 60\%$, (2) presence of respiratory distress, increased work of breathing, or altered consciousness based on the evaluation for the presence of chest movement, even with oxygen administration, (3) presence of unstable hemodynamics or multiple organ failure, or (4) rapid

deterioration of oxygenation within a few hours. The patients requiring IPPV were transferred to the intensive care unit (ICU) or another hospital.

2.4. Clinical assessment

The hospital's electronic medical records were used to extract data during hospitalization, such as symptoms, vital signs, ECG monitor findings, peripheral capillary oxygen saturation (SpO_2), oxygen demand, laboratory test results, computed tomography scans, and patient characteristics, including age (in years), sex, body mass index (BMI; in kg/m^2), smoking history (current or former), and comorbidities. The data on the number of days from onset to admission to our hospital, initiation and termination of COT, COT duration, initiation and termination of HFNC treatment, and HFNC treatment duration were evaluated. We followed the patients' oxygenation duration for a maximum of 30 days.

2.5. Evaluation of respiratory status before and after HFNC treatment initiation

We focused on the changes in RR to assess the respiratory status. We determined the degree of improvement in RR before and after HFNC treatment, calculated as $(\text{RR before HFNC treatment}/\text{RR after HFNC treatment}) \times 100$, and defined a value of ≥ 101 as RR improvement. The ROX index, calculated as $(\text{SpO}_2/\text{FiO}_2)/\text{RR}$, and a cutoff ROX index of 5.55 was used based on a study by Hu et al. [10]. In all the patients with COVID-19, the parameters to assess the respiratory status, including FiO_2 and RR, were determined twice a day, once in

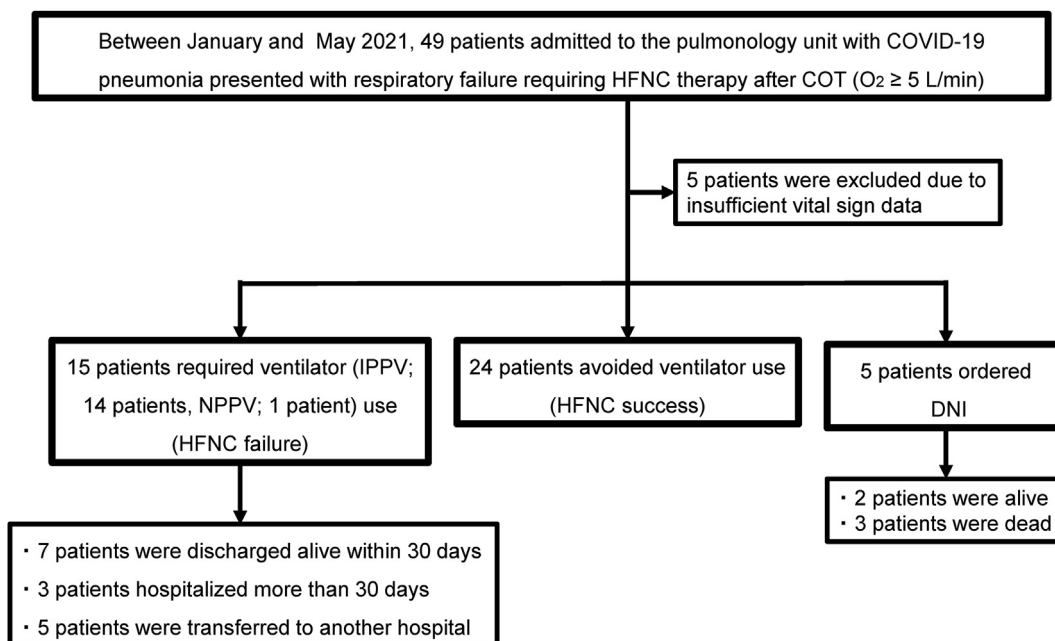


Fig. 1 – Study population flowchart. The final study cohort comprised 39 patients. COVID-19, coronavirus disease 2019; COT, conventional oxygen therapy; NPPV, noninvasive positive-pressure ventilation; IPPV, invasive positive-pressure ventilation; HFNC, high-flow nasal cannula; DNI, do not intubate.

the day shift and once in the night shift. The evaluation frequency was increased to more than four times a day in patients with an overt worsening of the clinical condition. In patients on nasal cannula, the FiO_2 was calculated by multiplying the amount of oxygen by 4 and adding 20. In patients using simple face masks, the FiO_2 was calculated by subtracting 1 from the administered amount of oxygen and multiplying by 0.1. In patients using reserved masks, the FiO_2 was calculated by multiplying by 0.1, with a maximum of 1.0 [12]. Additionally, the respiratory status of patients was evaluated at the time of initiating or switching the oxygen delivery devices, including HFNC. If available, the data recorded at a timepoint closest to 24 h after HFNC treatment initiation, were used. Otherwise, the data recorded 18–24 h after HFNC treatment initiation were used to represent 24-h values. The respiratory status immediately before intubation was evaluated in cases where intubation was performed less than 18 h after the HFNC treatment initiation.

2.6. Statistical analysis

The summary statistics were calculated for baseline variables using the mean (\pm standard deviation [SD]), median (interquartile range), frequency distributions, or proportions. The differences between the HFNC success and HFNC failure groups were analyzed. For continuous variables, we first compared the mean values (\pm SD) and quartiles between the two groups. Subsequently, the Kolmogorov–Smirnov test (2-sided) and Shapiro–Wilk test were used to test the normality, and homoscedasticity was further tested using the F-test. The Welch t-test and Mann–Whitney U test were performed according to the data distribution. For continuous variables, such as age, BMI, we first compared the mean values (\pm SD) and quartiles between the two groups. The Fisher exact test was used to determine the significance of differences in the proportions of the groups. After the key characteristics of the variables were studied, a logistic regression model was fitted with age, ROX index, and percentage improvement of RR. A p value < 0.05 was considered as statistically significant.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (a modified version of R commander designed to add statistical functions frequently used in biostatistics) [13].

2.7. Patient and public involvement

No patients were involved in determining the research questions, outcome measures, or study design. There was no patient input on the interpretation or the writing up of the results.

3. Results

3.1. Patient characteristics

Table 1 presents the clinical characteristics of the 39 patients in the study cohort (HFNC success group, $n = 24$, and HFNC failure group, $n = 15$). No significant differences in the characteristics (i.e., age, sex, BMI, and smoking history), comorbidities (i.e., hypertension, diabetes mellitus, dyslipidemia, and emphysema), or other laboratory findings were observed between the two groups.

3.2. Respiratory status and treatment before and after hospitalization

The respiratory status changes and treatment during hospitalization are shown in Fig. 2 and Table 2. The total duration of COT and HFNC treatments were significantly shorter in the HFNC success group than in the HFNC failure group ($p = 0.0003$ and $p < 0.001$, respectively). This suggests that the HFNC success group underwent early withdrawal of oxygen therapy compared with the HFNC failure group. There was no significant difference in the days from symptom onset to hospitalization; additionally, there was no significant difference between COT and HFNC treatment according to the day when

Table 1 – Characteristics and outcomes of the patient cohort.

Variables	All patients ($n = 39$)	HFNC success group ($n = 24$)	HFNC failure group ($n = 15$)	P value
Characteristics				
Age (years)	57.9 \pm 12.7	58.0 \pm 13.2	57.8 \pm 12.3	0.963
Sex (male)	35 (89.7%)	21 (87.5%)	14 (93.3%)	1
BMI (kg/m^2)	25.5 (24.0–28.3)	26.5 (24.1–28.3)	24.6 (23.4–28.2)	0.171
Smoking history	19 (48.7%)	11 (45.8%)	8 (53.3%)	0.748
Comorbid disease				
Hypertension	17 (43.6%)	11 (45.8%)	6 (40%)	0.753
Diabetes mellitus	11 (28.2%)	6 (25%)	5 (33.3%)	0.718
Dyslipidemia	11 (28.2%)	5 (20.8%)	6 (40%)	0.277
Emphysema	9 (23.1%)	5 (20.8%)	4 (26.7%)	0.711
Laboratory findings at admission				
C-reactive protein (mg/dL)	7.49 (5.12–13.92)	7.34 (4.61–11.84)	7.49 (5.95–14.68)	0.354
Procalcitonin (ng/mL)	0.12 (0.09–0.17)	0.12 (0.09–0.14)	0.13 (0.09–0.21)	0.166
Lactate dehydrogenase (U/L)	356 (316–409)	357 (319–402)	356 (321–478)	0.359
Ferritin (ng/dL)	668 (511–1055)	629 (465–962)	685 (540–1093)	0.548
D-dimer ($\mu\text{g}/\text{mL}$)	0.78 (0.63–0.96)	0.77 (0.58–0.96)	0.81 (0.68–0.99)	0.341

Data are presented as means \pm SD, medians (interquartile range), or numbers (%).
BMI, body mass index; HFNC, high-flow nasal cannula.

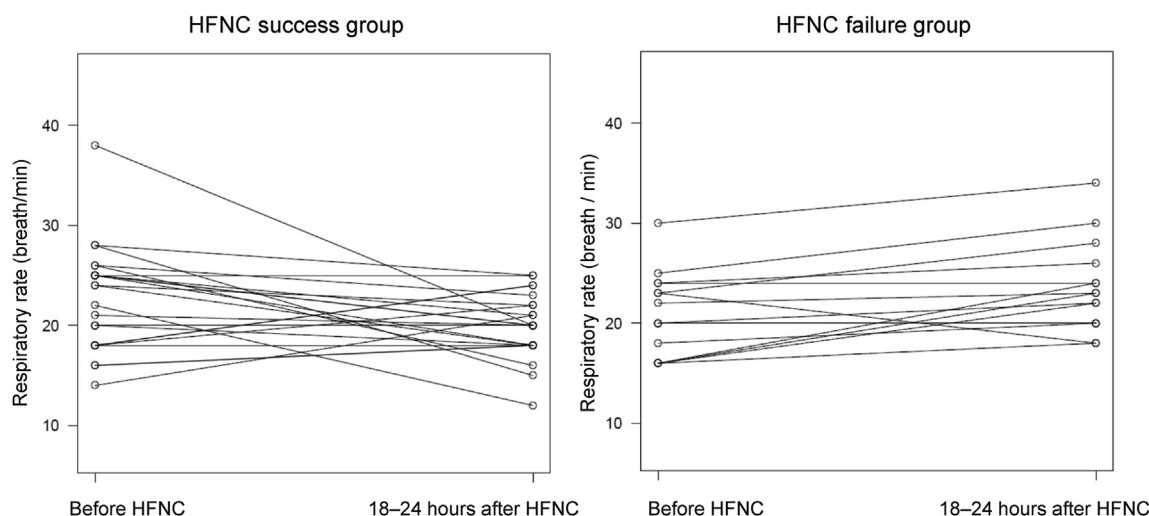


Fig. 2 – RR changes before and after HFNC treatment. The degree of improvement in RR between 0 and 6 h before HFNC treatment and between 18 and 24 h after HFNC treatment is shown. RR, respiratory rate; HFNC, high-flow nasal cannula.

oxygen therapy was initiated. The rate of patients treated with baricitinib or tocilizumab) compared with the standard (i.e., dexamethasone and remdesivir) treatment options did not significantly differ between the two groups (Table 2).

Fig. 3 shows the Kaplan–Meier curves (i.e., the process from hospitalization to the withdrawal of oxygen as a survival curve) indicating the probability of duration of oxygen administration for the HFNC success and the HFNC failure

groups. The survival analysis showed that the HFNC success group had a significantly shorter time to oxygen withdrawal ($p < 0.01$).

3.3. Changes in RR before and after HFNC treatment

The RR after HFNC treatment was significantly higher in the HFNC failure group than in the HFNC success group (Table 2,

Table 2 – Outcomes of patients during hospitalization.

Outcome	All patients (n = 39)	HFNC success group (n = 24)	HFNC failure group (n = 15)	P value
During hospitalization				
Symptom onset to admission (days)	7.0 (5.0–7.5)	7.0 (5.0–8.0)	6.0 (5.0–7.0)	0.804
COT initiation (day)	1.0 (1.0–2.0)	1.0 (1.0–2.3)	1.0 (1.0–1.0)	0.23
HFNC treatment initiation (day)	3 (2–4)	3 (2–4)	2 (1–3)	0.146
COT duration (days)	10.0 (8.5–17.0)	9.0 (8.0–11.0)	20.5 (17.3–30.0)	0.0003
HFNC treatment duration (days)	3.0 (1.5–4.5)	4.0 (3.0–6.0)	1.0 (1.0–2.0)	<0.001
Treatments				
Baricitinib/tocilizumab	21 (53.8%)	15 (62.5%)	6 (40%)	0.203
Respiratory parameters before HFNC treatment				
RR (breaths/min)	22 (18–25)	23 (18–25)	20 (17–24)	0.309
Respiratory parameters after HFNC treatment				
Flow (L/min)	45.0 (40–50) (NA in 1)	45.0 (40–50) (NA in 1)	50 (40–50)	0.676
RR (breaths/min)	20 (18–24)	20 (18–22)	23 (20–25)	0.00623
ROX index	7.74 (5.97–10.44) (NA in 3)	9.11 (7.33–10.67) (NA in 2)	5.74 (4.94–7.51) (NA in 1)	0.00027
ROX index ≥ 5.55	29 (80.6%) (NA in 3)	21 (95.5%) (NA in 2)	8 (57.1%) (NA in 1)	0.00833
(RR before HFNC treatment/RR after HFNC treatment) $\times 100$	100.0 (88.6–116.0)	110.1 (97.2–127.1)	90.0 (82.7–97.8)	0.0176
RR improvement	15 (38.5%)	14 (58.3%)	1 (6.7%)	0.00184

Data are presented as medians (interquartile range) or numbers (%).

P values < 0.05 were considered statistically significant.

The ROX index is defined as the ratio of SpO_2/FiO_2 to the RR.

COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; RR, respiratory rate; SpO_2 , oxygen saturation; FiO_2 , fraction of inspired oxygen; ROX index, respiratory rate-oxygenation index; NA, not available.

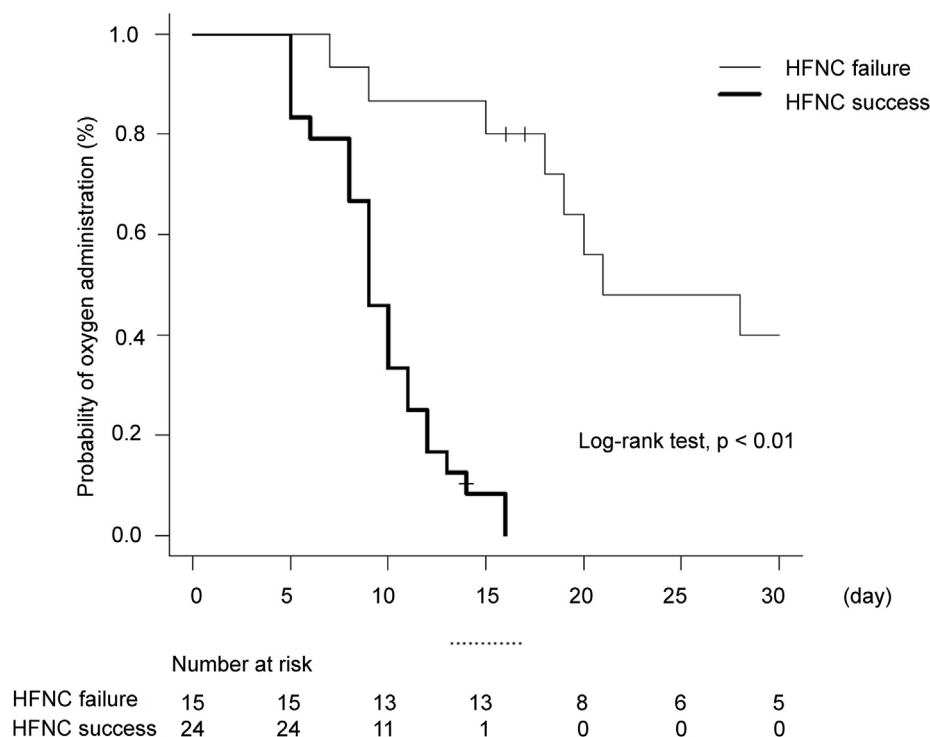


Fig. 3 – Duration from initiation to withdrawal of oxygen administration. The Kaplan–Meier curves indicate the probability of duration of oxygen administration for the HFNC success and the HFNC failure groups. The HFNC success group showed a significantly shorter time to oxygen withdrawal ($p < 0.01$). HFNC, high-flow nasal cannula.

$p = 0.00623$), whereas the RR before HFNC treatment did not significantly differ between the two groups. Regarding the changes in RR before and after the HFNC treatment in each group, the average RR value increased in the HFNC failure group, but decreased in the HFNC success group (Fig. 2). The RR in the HFNC success group was significantly lower than that in the HFNC failure group (Table 2, $p = 0.00166$).

3.4. ROX index

The ROX index before and after the HFNC treatment is shown in Table 2. The ROX index before the HFNC treatment did not significantly differ between the two groups, whereas the ROX index of the HFNC success group was significantly higher after the HFNC treatment than in the HFNC failure group ($p = 0.00027$). The frequency of a ROX index ≥ 5.55 was not significantly different between the two groups before the HFNC treatment, but was significantly higher in the HFNC success group after HFNC treatment than in the HFNC failure group.

3.5. Multivariate analysis for HFNC treatment success

Table 3 reports the odds ratios with 95% confidence intervals based on the logistic regression analysis of the HFNC success group, adjusting for factors, such as age, respiratory improvement, and a ROX index ≥ 5.55 . An improvement in the RR was associated with HFNC treatment success (odds ratio: 1.39, 95% confidence interval: 1.29–151).

3.6. Safety of healthcare providers

There were no apparent COVID-19 infections or infection clusters in healthcare providers caused by the transmission of COVID-19 by patients using HFNC treatment during the study period. All the patients were accommodated in rooms under negative pressure during hospitalization and always used surgical masks when healthcare providers were in the same room.

4. Discussion

Our study revealed several findings. First, a total of 24 of the 39 patients (62%) treated with HFNC therapy for ARF caused by COVID-19 pneumonia avoided intubation (i.e., HFNC treatment success). Second, an improved RR within 18–24 h of HFNC treatment initiation might have utility as an indicator of ventilator avoidance. Furthermore, a multivariate analysis demonstrated that even after adjusting for age and a ROX index ≥ 5.55 , the RR improvement was an influential factor for HFNC treatment success. Third, the HFNC treatment management shortened the COT duration.

Our findings indicated that RR improvement could be an indicator of ventilator avoidance during the HFNC treatment for ARF caused by COVID-19 pneumonia. RR assessment is one of the important clinical tools for determining the severity of a patient's condition with respiratory failure. In a multicenter prospective study comparing established prognostic scores such as the National Early Warning Score 2 (NEWS2), the

Table 3 – Multivariate analysis for HFNC treatment success.

Variables	OR (95% CI)	P value
Age (years)	1.04 (0.96–1.12)	0.3240
Respiratory rate improvement	13.90 (1.29–151.00)	0.0303
ROX index ≥ 5.55	7.80 (0.69–87.70)	0.0962

P values < 0.05 are considered to indicate statistical significance.
The ROX index is defined as the ratio of SpO₂/FiO₂ to the RR.
CI, confidence interval; OR, odds ratio; ROX index, respiratory rate-oxygenation index.

Quick Sequential (Sepsis-Related) Organ Failure Assessment score, and the Confusion, Urea, Respiratory Rate, Blood Pressure, and Age Above or Below 65 Years score (CURB-65), Bradley et al. demonstrates that these previous prognostic scores, including the assessment of RR, are not suitable in the setting of COVID-19, probably because these scores include both the respiratory status and circulatory status [14]. Furthermore, they suggest that new prognostic scores should be particularly focused on the respiratory status, such as the 4C mortality score, which includes eight variables readily available at the initial hospital assessment: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein [14,15]. In our study, the RR in patients requiring mechanical ventilation tended to increase even after the initiation of HFNC; indicating that RR fluctuations might simply affect the outcome, highlighting their importance.

Evaluating the RR reduction within 18–24 h seemed clinically reasonable to predict the success of the HFNC treatment in our study. Several reports have evaluated RR reduction within specific timeframes in patients with respiratory diseases treated by HFNC. From a physiological point of view, Bräunlich et al. revealed that RR was lowered right after using HFNC in healthy volunteers and in patients with COPD and idiopathic pulmonary fibrosis [16]. Sztrymf et al. reported that the RR significantly decreased over 48 h compared with before the initiation of HFNC treatment, whereas the patients who required ventilation were discontinued from HFNC within 4 h of initiating HFNC. Furthermore, the RR 45 min after the HFNC treatment initiation was significantly higher in the patients who required intubation or ventilation than in those who did not [17]. Based on these findings, HFNC treatment is expected to improve the RR; however, if an improvement in RR cannot be expected, it is vital to consider intubation and ventilation without hesitation. In this study, we examined whether or not the RR improved within 24 h after HFNC treatment initiation.

The HFNC success group had a significantly shorter duration of oxygen administration during hospitalization than the HFNC failure group, possibly indicating that unnecessary ventilator application may prolong the duration of COT. The Japanese Respiratory Society previously suggested the intubation or HFNC treatment for patients requiring oxygen administration of ≥ 5 L/min at the beginning of the COVID-19 pandemic (March 2020); however, the fact is that some facilities do not use HFNC treatment from the viewpoint of aerosol transmission. Nevertheless, there is no evidence that the risk of HFNC treatment is particularly high compared with normal breathing and COT [18,19]. Additionally, a recent

questionnaire administered to certified hospitals in Japan revealed that pulmonologists selected HFNC treatment more frequently than before when treating patients with COVID-19 [6]. Moreover, the HFNC success group achieved oxygen withdrawal in a significantly shorter time. Our study suggests that the safe use of HFNC treatment may prevent the use of ventilators in patients who would otherwise be intubated.

The validated ROX index is known as a tool to predict the outcome of HFNC treatment (need or no need for intubation) for respiratory failure in the current clinical setting. Roca et al. reported that the ROX index ≥ 4.88 measured at 2, 6, or 12 h after HFNC treatment initiation was consistently associated with a lower risk for intubation in patients with pneumonia with acute respiratory failure (not including COVID-19 pneumonia) [20]. Most recently, various ROX index cutoff values have been reported in COVID-19; however, the values by several studies are inconsistent [10,11]. Although the ROX index cutoff was set to 5.55 in our multivariate analysis based on a retrospective cohort study of hypoxemic patients with COVID-19 [10], RR improvement had a greater effect on the HFNC treatment success than the ROX index. We speculate that this was due to an inappropriate cutoff ROX index value or that the RR was simply a better index (less confounding) than a ROX index ≥ 5.55 for our patient population.

Our study has several limitations. First, because it was a single-center study, only a small number of patients were included. Second, this was a retrospective study. It has been reported that the use of HFNC treatment in the 3rd pandemic wave in Japan has increased compared with the 1st wave (49% vs. 12%) [5], and further data collection is desired in the future. Third, the RR before HFNC initiation was relatively low in the present study compared to the previous reports. In a study by Roca et al., HFNC was initiated for the patients who were unable to maintain an SpO₂ above 92% and an RR of ≥ 25 breaths/min while receiving standard oxygen of ≥ 10 L/min by a face mask [20]. In contrast, HFNC was initiated in patients who required oxygen administration of ≥ 5 L/min in the present study according to the recommendation of the clinical management guide of patients with COVID-19 by the Ministry of Health, Labour, and Welfare, which might explain the lack of respiratory distress observed at the time of HFNC treatment initiation. Fourth, the ROX index cutoff value to 5.55. Because the cutoff value of the ROX index varies between reports, we adopted the cutoff value of 5.55 based on the report by Hu et al. [10]. They compared the ROX index measurements at 2, 6, 12, and 24 h after the HFNC treatment initiation and concluded that the ROX index 6 h after the start of HFNC treatment was the most useful for determining the treatment effect [10]. Fifth, the ROX index used in the present study was higher than that utilized in previous studies. This might be partly explained by our intubation criteria switching from HFNC to the ventilator for the patients (shown in Methods part). Furthermore, the patients transitioned from HFNC treatment to noninvasive positive-pressure ventilation might have biased our results in the present study. However, such patients were only one; therefore, the effect of noninvasive positive-pressure ventilation on the ROX index might have been small. Sixth, in the present study, RR improvement was primarily evaluated 18–24 h after the initiation of HFNC treatment. Although Roca et al. reported that the ROX index

measured at 2, 6, or 12 h after HFNC treatment initiation was consistently associated with a lower risk for intubation [20], it was not possible to evaluate the respiratory status frequently in the present study where all the patients treated with HFNC were in non-intensive care unit settings and the respiratory status was primarily evaluated twice a day, with the evaluation frequency depending on the symptom severity.

In conclusion, HFNC treatment certainly appears useful to avoid ventilation and allows for the quick withdrawal of oxygen administration. In this clinical setting, RR improvement may be a convenient, useful, and universal indicator of the success of HFNC treatment.

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Authors' contributions

Study conception and design: Y.T., J.T., Y.H., and K.T. Data collection, analysis, and review: Y.T. and J.T. Statistical analysis and interpretation: Y.T., J.T., and Y.H. Administrative and technical support: Y.T., J.T., Y.H., and K.T. Drafting of the manuscript: Y.T. and J.T. Critical revision of the manuscript: Y.T., J.T., Y.H., T.K., H.T., K.K., T.K., Y.I., Y.S., and K.T.

Conflict of Interest

J.T. has received research funding from Teijin Pharma Ltd as part of a collaborative research project with Chiba University and Teijin Pharma Ltd. Other authors report no conflicts of interest.

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