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High-flow nasal cannula for severe COVID-19 patients in a Japanese single-center, retrospective, observational study: 1 year of clinical experience

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Abstract: High-flow nasal cannula (HFNC) can be effective in treating type 1 respiratory failure by reducing the severity of coronavirus disease 2019 (COVID-19). The purpose of this study was to assess the reduction of disease severity and safety of HFNC treatment in patients with severe COVID-19. We retrospectively observed 513 consecutive patients with COVID-19 admitted to our hospital from January 2020 to January 2021. We included patients with severe COVID-19 who received HFNC for their deteriorating respiratory status. HFNC success was defined as improvement in respiratory status after HFNC and transfer to conventional oxygen therapy, while HFNC failure was defined as transfer to non-invasive positive pressure ventilation or ventilator, or death after HFNC. Predictive factors associated with failure to prevent severe disease were identified. Thirty-eight patients received HFNC. Twenty-five (65.8%) patients were classified in the HFNC success group. In the univariate analysis, age, history of chronic kidney disease (CKD), non-respiratory sequential organ failure assessment (SOFA) ≥ 1, oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) before HFNC ≤ 169.2, were significant predictors of HFNC failure. Multivariate analysis revealed that SpO_2/FiO_2 value before HFNC ≤ 169.2 was an independent predictor of HFNC failure. No apparent nosocomial infection occurred during the study period. Appropriate use of HFNC for acute respiratory failure caused by COVID-19 can reduce the severity of severe disease without causing nosocomial infection. Age, history of CKD, non-respiratory SOFA before HFNC ≤ 1, and SpO_2/FiO_2 before HFNC ≤ 169.2 were associated with HFNC failure.

***Keywords*:** COVID-19, SARS-CoV-2, acute respiratory failure, high flow nasal cannula

Introduction

It has been more than 2 years since the start of the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). While the pandemic is expected to be resolved as the vaccination rate increases, the emergence of highly infectious variant strains suggests that it will take some time for the pandemic to fully subside. To cope with the emergence of this novel coronavirus, socioeconomic activities must be restricted when necessary. However, lifting these restrictions leads to the spread of infection. This means that it is important to reduce disease severity in severe cases of COVID-19 to avoid excessive pressure on the healthcare system.

High-flow nasal cannula (HFNC) has been shown to be effective in treating type 1 respiratory failure and is expected to reduce disease severity in patients with COVID-19 (*1*). Even though HFNC was previously not recommended because of concerns about the risk of aerosol generation, a recent shift in opinion now considers HFNC treatment in the appropriate environment an effective method of choice. We previously published the treatment outcomes of HFNC administered between January and September 2020 and reported the possibility of a reduction of disease severity in severe COVID-19 cases, as well as increased safety (*2*). The purpose of this study was to expand the study period to 1 year and report the outcomes of HFNC treatment in patients with severe COVID-19 at our institution.

Patients and Methods

Study design and patients

From January 2020 to January 2021, we retrospectively

analyzed 513 consecutive patients with COVID-19 who were admitted to our hospital. We included patients with severe COVID-19 who received HFNC treatment owing to their worsening respiratory status in spite of conventional oxygen therapy. Disease severity was classified by National Institutes of Health criteria (*3*). HFNC success was defined as improvement in respiratory status and transfer to conventional oxygen therapy, while HFNC failure was defined as transfer to non-invasive positive pressure ventilation (NPPV) or ventilator, or death after treatment. Patients who died without intubation due to do-not-attempt-resuscitation (DNAR) orders were classified as HFNC failure. Patients who had HFNC attached for weaning either after extubation or withdrawal of NPPV were excluded.

Setting of HFNC

In our hospital's operation, HFNC was placed when the saturation of percutaneous oxygen (SpO_2) was below 93% even with nasal cannula or oxygen mask on oxygen flow rate of 6 L/min or more. The fraction of inspired oxygen (FiO_2) was determined by considering the oxygen delivery device and oxygen dosage prior to HFNC placement. The flow rate was adjusted in the range of 30-60 L/min depending on oxygenation and the patient's comfort level. The F&P 850 system (Fisher & Paykel Healthcare, Auckland, New Zealand) was used to provide HFNC therapy. The HFNC gas temperature was set at 31 °C (humidity: 32 mg/L) or 37 °C (humidity: 44 mg/L), depending on the patient's preference.

Environment during HFNC therapy

All patients who were administered HFNC used a private negative pressure room. Staff providing COVID-19 medical treatment underwent donning and doffing training of personal protective equipment beforehand. The medical care staff donned the personal protective equipment, including long-sleeved gowns, gloves, N95 masks, surgical masks with face shields, and hair caps, while attending to patients with HFNC as well as conventional oxygen therapy. There was no restriction on the frequency of entry into the HFNC treatment area. The patients were instructed to wear a surgical mask as much as possible during medical examination and care.

Data Collection

All data were retrospectively collected from electronic medical records. Recorded data included demographics (age, gender, body mass index), vital signs (body temperature, respiratory rate, heart rate, blood pressure, saturation of percutaneous oxygen), comorbidity, smoking status, detailed data related to HFNC use, and baseline treatment for COVID-19. The ratio of SpO_2/FiO_2 and the respiratory rate-oxygenation (ROX) index were collected as respiratory status before HFNC treatment. The ROX index was defined as the ratio of SpO_2/FiO_2 to respiratory rate. Glasgow Coma Scale, non-respiratory sequential organ failure assessment (SOFA), and quick SOFA (qSOFA) were also collected as assessment scores. The scores on admission day and before use of HFNC were calculated using the worst values observed within 6 hours after admission and 24 hours prior to HFNC treatment.

Statistical analyses

Descriptive statistics were used to summarize the baseline characteristics and to compare the success and failure rates of HFNC. Continuous variables were presented as medians (interquartile range), and binary variables were presented as numbers and frequencies (percentages). Continuous variables were compared using the Mann–Whitney *U*-test, and binary variables were compared using the Fisher's exact test. Vital signs and respiratory status before the attachment of HFNC and 2–6 hours after the attachment of HFNC were compared using Wilcoxon signed-rank test. To identify the predictors of HFNC failure, a univariate analysis was performed using baseline characteristics with $p < 0.2$. The receiver operating characteristic (ROC) curve analyses were performed to assess the cutoff values for the HFNC outcomes, which are the non-respiratory SOFA and SpO_2/FiO_2 before the attachment of HFNC. The area under the ROC curve (AUROC) was calculated as a measure of predictive capacity. A multivariate analysis was performed using logistic regression analysis, incorporating variables with $p < 0.05$ from the univariate analysis. Odds ratio (OR) were calculated along with 95% confidence interval (CI). A two-tailed *p*-value of < 0.05 was considered significant. All statistical analyses were performed using EZR (ver. 1.54; Jichi Medical University, Saitama, Japan).

Ethical approval

The National Center for Global Health and Medicine ethics review committee approved this study (NCGM-G-004024-00). The protocol for the research project conforms to the provisions of the Declaration of Helsinki for experiments involving humans.

Results

Thirty-eight patients received HFNC treatment due to worsening respiratory status. The median age was 66 years, and 30 patients (78.9%) were men. Baseline treatment consisted mostly of remdesivir, steroids, and heparin. Of the 38 patients who underwent HFNC therapy, 25 (65.8%) patients were subsequently transferred to conventional oxygen therapy and classified in the HFNC success group. However, the other 13

(34.2%) patients became critically ill (Figure 1). The median age of the patients in the HFNC success group was 59 years, which was significantly less than that of the patients in the HFNC failure group (74 years) (p = 0.008). Regarding comorbidities, the rate of chronic kidney disease (CKD) was significantly higher in the HFNC failure group (46.2% *vs*. 4%; p = 0.004). The median time from the onset of symptoms to the attachment of HFNC was 9 days in both groups. There were no differences in the body mass index, smoking history, or baseline treatment between the two groups. There was no difference in qSOFA before HFNC treatment between the two groups, while non-respiratory SOFA before HFNC use was significantly higher in the HFNC failure group (2 *vs*. 0, p = 0.0005). Regarding the vital signs and respiratory status before the attachment of HFNC, the SpO_2/FiO_2 was significantly lower in the HFNC failure group than in the HFNC success group (117.5 *vs.* 169.2, p = 0.01). The respiratory rate oxygenation (ROX) index also tended to be lower in the HFNC failure group (5.7 *vs.* 6.3, p = 0.28). In contrast, the heart rate (HR) and respiratory rate (RR) tended to be higher in the HFNC success group. Three (12%) patients in the HFNC success group and five (38.5%) patients in the HFNC failure group had DNAR orders (Table 1). Two to six hours after HFNC was attached, the RR worsened from 22 to 24.5 in the HFNC failure group (p = 0.62) but significantly improved from 24 to 22 in the HFNC success group (p = 0.009) (Figure 2A). Moreover, the HR changed from 87 to 85 in the HFNC failure group and significantly improved from 94 to 74 in the HFNC success group (p < 0.0001) (Figure 2B). Both groups showed improvement in the SpO_2/FiO_2 ratio, and the improvement in the HFNC success group from 169.2 to 192 was significant (p = 0.004) (Figure 2C). The ROX index rose slightly from 5.7 to 6.0 in the HFNC failure group (p = 0.3) and significantly improved from 6.3 to 9.5 in the HFNC success group (p = 0.0004) (Figure 2D).

Seven of the 13 patients in the HFNC failure group were directly placed on ventilators. Four patients were placed on NPPV after HFNC use, and two continued HFNC treatment until death (Table 1). The median durations of HFNC treatment in the HFNC success and failure groups were 5 days and 3.5 days, respectively, while the maximum FiO_2 was 60% and 100%, respectively. Eventually, seven patients (53.8%) in the HFNC failure group died, and four of those died without intubation following the DNAR order. As for the main cause of death, three patients had COVID-19-associated pneumoniae, two had acute respiratory distress syndrome due to secondary bacterial infection, one had acute kidney injury, and one had acute exacerbations of interstitial pneumoniae (Table 2).

Using the ROC curve, the best cutoff for non-respiratory SOFA was estimated to be 1.0 with a sensitivity of 0.92, specificity of 0.615, and AUROC of 0.815. The best cutoff of SpO_2/FiO_2 was 169.2 with a sensitivity of 0.520, specificity of 0.923, and AUROC of 0.758. In the univariate analysis, age (OR = 1.08; 95% CI: 1.02–1.15; p = 0.012), history of CKD (OR = 20.6; 95% CI: 2.11–201.0; p = 0.009), non-respiratory SOFA before HFNC ≥ 1 (OR = 10.6; 95% CI: 2.17–51.4; p

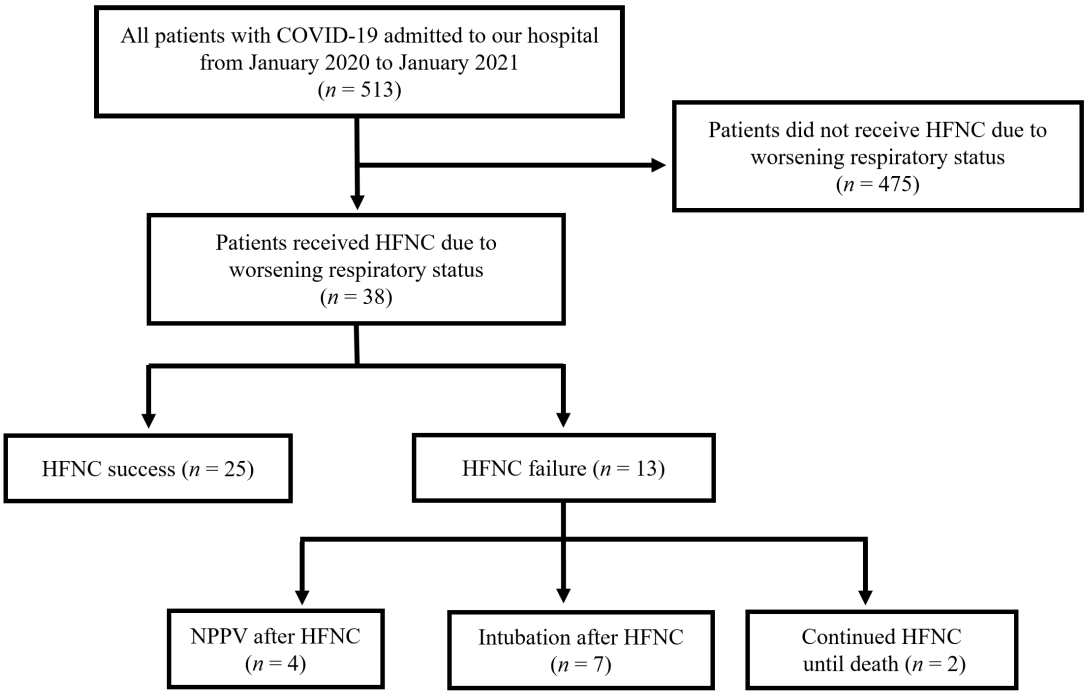

Figure 1. Flow diagram and clinical outcome of patients. COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; NPPV, non-invasive positive pressure ventilation.

Table 1. Baseline characteristics of patients who were administered HFNC therapy due to deterioration

Variables	Total (*n* = 38)	HFNC success (*n* = 25)	HFNC failure (*n* = 13)	*p*
Age (years), median (IQR)	66 (51-75)	59 (50-70)	74 (68-82)	0.008
Gender (Male), *n* (%)	30 (78.9%)	22 (88%)	8 (61.5%)	0.094
Body mass index (kg/m^2), median (IQR)	26.8 (22.6-30.2)	26.6 (24.2-30.6)	27.2 (22.3-28.8)	0.43
Comorbidity				
Hypertension	23 (60.5%)	13 (52%)	10 (76.9%)	0.18
Diabetes mellitus	19 (50%)	12 (48%)	7 (53.8%)	1
Dyslipidemia	11 (28.9%)	6 (24%)	5 (38.5%)	0.46
Asthma	3 (7.9%)	3 (12%)	0	0.54
Coronary heart disease	3 (7.9%)	2 (8%)	1 (7.7%)	1
Chronic kidney disease	7 (18.4%)	1 (4%)	6 (46.2%)	0.004
Immunosuppression	1 (2.6%)	0	1 (7.7%)	0.34
Smoking status				
Never smoker	14 (36.8%)	11 (44%)	3 (23.1%)	0.29
Current or former smoker	24 (63.2%)	14 (56%)	10 (76.9%)	0.29
Baseline treatment				
Remdesivir, *n* (%)	31 (81.2%)	22 (88%)	9 (69.2%)	0.20
Hydroxychloroquine, *n* (%)	3 (7.9%)	1 (4%)	2 (15.4%)	0.27
Favipiravir, *n* (%)	8 (21%)	7 (28%)	1 (7.7%)	0.22
Tocilizumab, *n* (%)	2 (5.3%)	1 (4%)	1 (7.7%)	1
Lopinavir-ritonavir, *n* (%)	1 (2.6%)	0	1 (7.7%)	0.34
Steroid, *n* (%)	37 (97.4%)	25 (100%)	12 (92.3%)	0.34
Heparin, *n* (%)	32 (84.2%)	23 (92%)	9 (69.2%)	0.15
PMX-DHP, *n* (%)	7 (18.4%)	5 (20%)	2 (15.4%)	1
Convalescent plasma therapy, *n* (%)	3 (7.9%)	2 (8%)	1 (7.7%)	1
Implementation of HFNC				
Days after onset (days), median (IQR)	9 (7-11.8)	9 (8-12)	9 (6-11)	0.66
Days after admission (days), median (IQR)	2 (1-2)	2 (1-2)	2 (1-3)	0.50
Severity score before HFNC, median (IQR)				
Glasgow Coma Scale, median (IQR)	15 (15-15)	15 (15-15)	15 (15-15)	NA
qSOFA, median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.81
non-respiratory SOFA, median (IQR)	0 (0-1.75)	0 (0-0)	2 (1-3)	0.0005
Vital signs and respiratory status before HFNC				
Systolic blood pressure (mmHg), median (IQR)	115.5 (105.3-124.8)	118 (107-127)	109 (100-117)	0.093
HR (bpm), median (IQR)	93 (82.3-102.5)	94 (91-95)	87 (83-100)	0.83
RR (/min), median (IQR)	24 (20.5-28)	24 (22-28)	22 (20-24)	0.14
SpO_2/ FiO_2, median (IQR)	154.2 (108.5-176)	169.2 (132.9-184.6)	117.5 (103.3-153.3)	0.01
ROX index, median (IQR)	6.3 (5.1-7.5)	6.3 (5.1-7.7)	5.7 (5.0-6.9)	0.28
DNAR, *n* (%)	8 (21.1%)	3 (12%)	5 (38.5%)	0.094

HFNC, high-flow nasal cannula; IQR, interquartile range; qSOFA, quick sequential organ failure assessment; PMX-DHP, polymyxin-B direct hemoperfusion; HR, heart rate; RR, respiratory rate; SpO_2, saturation of percutaneous oxygen; FiO_2, fraction of inspired oxygen, ROX index; respiratory rate-oxygenation index; DNAR, do-not-attempt-resuscitation.

= 0.004), and SpO_2/FiO_2 before HFNC ≤ 169.2 (OR = 13.0; 95% CI: 1.46–116.0; p = 0.021) were found to be statistically significant predictors of HFNC failure. We performed a multivariate analysis and calculated the adjusted ORs by incorporating variables with $p < 0.05$. Multivariate analysis revealed that an SpO_2/FiO_2 ratio ≦ 169.2 (adjusted OR = 15.9, 95% CI: 1.07–236.0, p = 0.004) before HFNC treatment was an independent predictor of HFNC failure (Table 3).

The medical staff treating patients with COVID-19, with or without HFNC, implemented airborne and contact infection control measures, including the use of N95 masks. No restrictions were placed on the frequency of entry into the HFNC treatment area. When HFNC apparatuses were attached, all patients were managed in negative-pressure individual rooms to prevent nosocomial infection resulting from aerosol production. No apparent nosocomial infection occurred during the study period.

Discussion

The risk of nosocomial infection poses a concern when the aerosol-generating device, HFNC, is applied to patients with COVID-19. However, our retrospective study showed that with a conducive environment, appropriate equipment, proper procedure, and infection control measures, it was possible to prevent 65.8% of severely ill patients from further deterioration of their condition without causing obvious nosocomial infections of COVID-19.

Previous studies have shown that HFNC treatment results in a lower intubation rate than noninvasive ventilation and standard oxygen therapy in patients with acute respiratory failure (*1*). HFNC has also been shown to be effective for managing acute respiratory failure caused by COVID-19 for the following reasons. Two phenotypes of COVID-19 pneumonia have been identified (*4*). As the disease progresses from Type L to

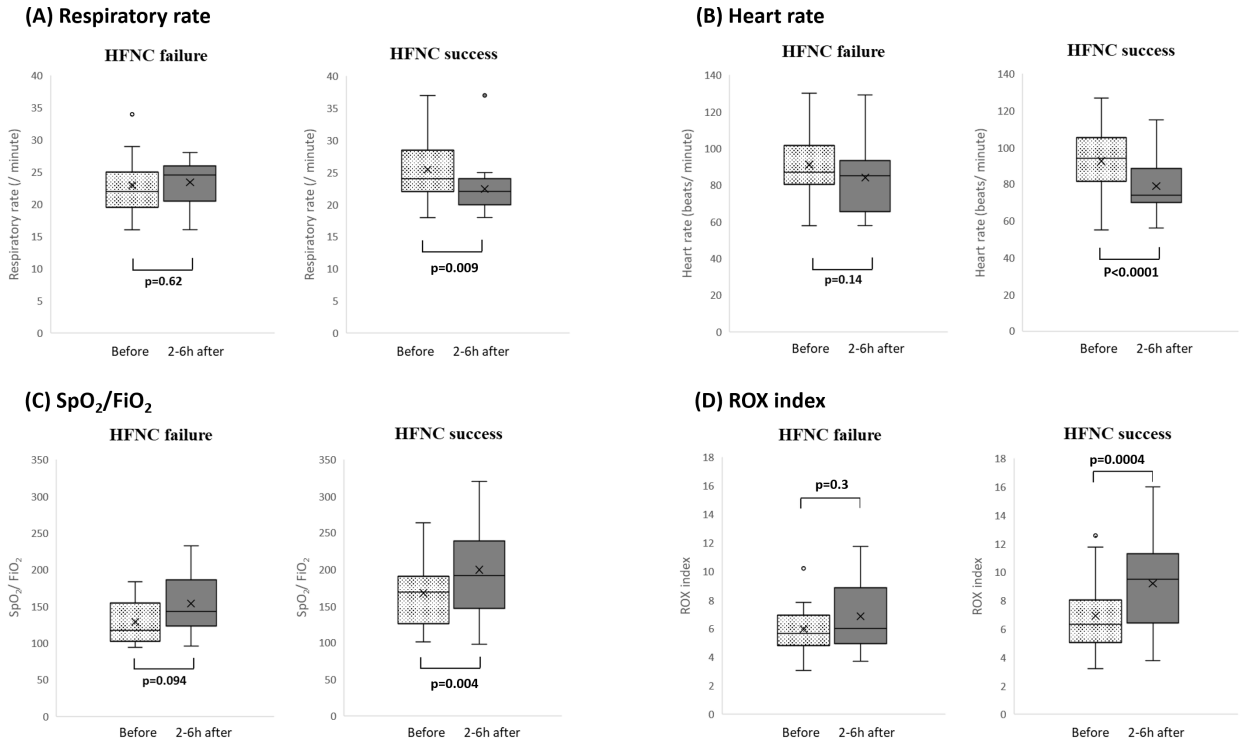

Figure 2. Sequential change of vital signs and respiratory status two to six hours after high-flow nasal cannula (HFNC) therapy. (A) The respiratory rate worsened from 22 (20-24) to 24.5 (21.5-26) in the HFNC failure group ($p = 0.62$) and improved from 24 (22-28) to 22 (20-24) in the HFNC success group ($p = 0.009$). **(B)** The heart rate changed from 87 (83-100) to 85 (71-93) in the HFNC failure group ($p = 0.14$) and improved from 94 (82-105) to 74 (70-86) in the HFNC success group ($p < 0.0001$). **(C)** The oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) changed from 117.5 (103.3-153.3) to 143.1 (124-184) in the HFNC failure group ($p = 0.094$) and improved from 169.2 (132.9-184.6) to 192 (155-237.5) in the HFNC success group ($p = 0.004$). **(D)** The respiratory rate-oxygenation index (ROX) index slightly rose from 5.7 (5.0-6.9) to 6.0 (5.3-8.0) in the HFNC failure group ($p = 0.3$) and improved from 6.3 (5.1-7.7) to 9.5 (6.6-11.3) in the HFNC success group ($p = 0.0004$). All data are presented as medians (interquartile range). HFNC, high-flow nasal cannula; SpO_2, saturation of percutaneous oxygen; FiO_2, fraction of inspired oxygen, ROX index; respiratory rate-oxygenation index.

Table 2. Treatment details and clinical outcome of HFNC therapy

Variables	HFNC success ($n = 25$)	HFNC failure ($n = 13$)
Duration of HFNC (days), median (IQR)	5 (3-6)	3.5 (2-7.3)
Time to NPPV or intubation from HFNC		
< 24/ < 48/ < 72/ ≥ 72 (hours), *n*	NA	5/ 1/ 3/ 2
Setting of HFNC		
Maximum flow rates (L/min), median (IQR)	50 (40-50)	60 (50-60)
Maximum FiO_2 (%), median (IQR)	60 (50-75)	100 (100-100)
Death, *n* (%)	0	7 (53.8%)
DNAR, *n*	NA	4
The main cause of death		
COVID-19 pneumoniae	NA	3
ARDS due to secondary bacterial infection	NA	2
Acute kidney injury	NA	1
Acute exacerbation of interstitial pneumonia	NA	1

HFNC, high-flow nasal cannula; NPPV, non-invasive positive pressure ventilation; IQR, interquartile range; FiO_2, fraction of inspired oxygen; DNAR, do-not-attempt-resuscitation; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome.

Type H, respiratory distress increases due to decreased lung compliance, increased dead space, increased atelectasis, carbon dioxide retention, fatigue, and anxiety. At that point, the respiratory center is stimulated through various chemoreceptors and mechanoreceptors in the respiratory physiology, causing a strong respiratory drive (*5*). Strong spontaneous breathing increases transpulmonary pressure and causes patient self-inflicted lung injury (*6.*).

In addition to disease severity and intravascular microthrombosis, self-inflicted lung injury is also known to be closely related to COVID-19 pneumonia. Therefore, HFNC can be used to target the positive end-expiratory pressure-like effect, improvement of oxygenation, and washout effect of CO_2. Although pain and emotional stimuli from the hypothalamus also transmit stimuli to the respiratory center, HFNC is superior to NPPV in terms of comfort (*1*). In the present study, HFNC was attached to all patients as there was no problem associated with the tolerability. Other advantages of HFNC include facilitation of eating, drinking, talking, oral care, rehabilitation, and performing awake self-proning.

There have been several reports on HFNC treatment

Table 3. Multivariate logistic regression analysis for the predictors of HFNC failure

Variables	Univariate Odds ratio (95% CI)	*p* value	Multivariate Odds ratio (95% CI)	*p* value
Age	1.08 (1.02-.)	0.012	1.06 (0.98-1.15)	0.13
Gender, male	0.22 (0.04-1.13)	0.07		
CKD, presence	20.6 (2.11-201.0)	0.009	8.25 (0.55-124.0)	0.13
Hypertension, presence	3.08 (0.68-13.9)	0.15		
Non-respiratory SOFA before HFNC <1	Ref.			
≥ 1	10.6 (2.17-51.4)	0.004	3.89 (0.48-31.7)	0.2
Systolic blood pressure before HFNC	0.97 (0.92-1.02)	0.18		
RR before HFNC	0.89 (0.76-1.04)	0.15		
SpO_2/ FiO_2 ratio before HFNC >169.2	Ref.			
≤ 169.2	13.0 (1.46-116.0)	0.021	15.9 (1.07-236.0)	0.004

HFNC, high-flow nasal cannula; CI, Confidence interval; CKD, Chronic kidney disease; SOFA, sequential organ failure assessment; RR, respiratory rate; SpO_2, saturation of percutaneous oxygen; FiO_2, fraction of inspired oxygen; ROX index; respiratory rate-oxygenation index; Ref, Reference.

for patients with COVID-19 in clinical practice. A significant lower rate of ventilator placement on day 28 was reported in the patients who received HFNC than the patients who did not at four sites in Paris, France (56% *vs.* 75%, $p < 0.001$) (*7*). A report from Temple University in the United States showed a 67% intubation avoidance rate in the HFNC group of patients with moderate-to-severe hypoxemic respiratory failure, which is very similar to the data reported in this study (*8*).

In this study, we used the SpO_2/FiO_2 ratio to evaluate the results because this was not a prospective observational study. The timing of arterial blood gas collection was determined by individual clinicians, and there were many missing data. According to Rice *et al.*, the SpO_2/FiO_2 ratio threshold of 235 identified PaO_2/FiO_2 ratio ≤ 200 with a sensitivity of 85% and a specificity of 85% (*9*). The baseline SpO_2/FiO_2 ratio for the entire study was 154.2, which is considered less than PaO_2/FiO_2 ratio of 200 and is relatively close to the value reported by Patel *et al*. (*8*). In this study, the baseline ROX index before HFNC was 6.3, which was higher than that reported by Richard Mellado-Artigas *et al.* (*10*). Since our previous report considered that early introduction of HFNC could lead to prevention of patient self-inflicted lung injury, it is possible that the current study may have resulted in an earlier introduction of HFNC than other reports (*2*). In the early stages of acute respiratory failure due to COVID-19, respiratory center drive may not occur, and the RR – the denominator of the ROX index – may not increase because lung compliance is not decreased (*5*).

Regarding predictors of HFNC failure, a prospective multicenter cohort study in Spain, involving patients with acute respiratory failure admitted to the intensive care unit, reported that non-respiratory SOFA and ROX indices were the main predictors of intubation in the multivariate analysis (*10*). According to a report by Patel *et al.,* SpO_2/FiO_2 ratio (<100) and history of CKD were predictors of HFNC failure (*8*). Consistent with their findings, the univariate analysis of the present study showed that a history of CKD and SpO_2/FiO_2 (≤ 169.2) were statistically significant predictors of HFNC failure. A possible explanation for the failure of the ROX index before HFNC treatment to be a predictor of HFNC failure in the present study might be the influence of the lower RR values in the HFNC failure group. This might have occurred because of "silent or happy hypoxia", which can lead to rapid clinical deterioration in patients with COVID-19 (*5*). Two to six hours after HFNC was attached, the RR worsened in the HFNC failure group but significantly improved in the HFNC success group. Thus, it may be important to monitor changes in the RR in patients receiving HFNC therapy.

Regarding the safety of HFNC for patients with COVID-19, the risk of nosocomial infection cannot be completely eliminated because HFNC is classified as a type of aerosol-generating procedure similar to NPPV. While our initial approach toward the use of HFNC treatment was cautious, with greater accumulation of data clarifying its efficacy and safety in patients with COVID-19, guidelines in various countries have begun to accept the use of HFNC treatment provided that infection control measures are thoroughly implemented in an appropriate environment. Among these, HFNC has been considered superior to conventional oxygen therapy and NPPV in the Surviving Sepsis Campaign Guideline (*11*). The results of the simulation also showed that the droplet diffusion distance was shorter with HFNC compared to reservoir masks and Venturi masks (*12*). However, there are reports of simulation results showing that the aerosol diffusion distance increases when the HFNC is loosely attached at a flow of 60 L/min. Therefore, the appropriate use of the HFNC is critical (*13*). As a result of the appropriate use and proper environmental measures, no apparent nosocomial infection occurred in our facility throughout the study period.

This study has several limitations. First, this study was retrospective, and the treatment setting was not unified. Variability in vital signs and respiratory parameters can occur before initiating HFNC because

there is no standard protocol for initiating HFNC treatment. Remdesivir, steroids, and heparin were administered in most patients; however, the type and amount of steroids varied according to the clinical physician's discretion, which can be a confounding factor. Furthermore, we had to substitute SpO_2/FiO_2 for PaO_2/FiO_2 ratio because the arterial blood gas analysis was not performed with appropriate timing. A unified protocol for HFNC use and medical treatment is necessary, and arterial blood gas analysis should be appropriately performed. Second, a prediction model for HFNC failure was not derived because the number of cases that received HFNC treatment were too few to prepare a validation dataset.

In conclusion, the appropriate use of HFNC treatment for COVID-19 patients with acute respiratory failure can reduce the severity of disease in severe patients without causing nosocomial infections. Age, prior history of CKD, non-respiratory SOFA before HFNC ≥ 1, and SpO_2/FiO_2 before HFNC ≤ 169.2 were predictive variables associated with HFNC failure. In the future, it will be necessary to assess the validity of the prediction variables for HFNC outcomes in a large-scale group study. Moreover, further accumulation of data on COVID-19 and other emerging infectious diseases are necessary.

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