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Pulse oximetric saturation to fraction of inspired oxygen (SpO_2/FIO_2) ratio 24 hours after high-flow nasal cannula (HFNC) initiation is a good predictor of HFNC therapy in patients with acute exacerbation of interstitial lung disease

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Abstract

Background: High-flow nasal cannula (HFNC) oxygen therapy provides effective respiratory management in patients with hypoxemic respiratory failure. However, the efficacy and tolerability of HFNC for patients with acute exacerbation of interstitial lung disease (AE-ILD) have not been established. This study was performed to assess the efficacy and tolerability of HFNC for patients with AE-ILD and identify the early predictors of the outcome of HFNC treatment.

Methods: We retrospectively reviewed the records of patients with AE-ILD who underwent HFNC. Overall survival, the success rate of HFNC treatment, adverse events, temporary interruption of treatment, discontinuation of treatment at the patient's request, and predictors of the outcome of HFNC treatment were evaluated.

Results: A total of 66 patients were analyzed. Of these, 26 patients (39.4%) showed improved oxygenation and were successfully withdrawn from HFNC. The 30-day survival rate was 48.5%. No discontinuations at the patient's request were observed, and no serious adverse events occurred. The pulse oximetric saturation to fraction of inspired oxygen (SpO_2/FIO_2) ratio 24 h after initiating HFNC showed high prediction accuracy (area under the receiver operating characteristic curve, 0.802) for successful HFNC treatment. In the multivariate logistic regression analysis, an SpO_2/FIO_2 ratio of at least 170.9 at 24 h after initiation was significantly associated with successful HFNC treatment (odds ratio, 51.3; 95% confidence interval, 6.13–430; $p < 0.001$).

Conclusions: HFNC was well tolerated in patients with AE-ILD, suggesting that HFNC is a reasonable respiratory management for these patients. The SpO_2/FIO_2 ratio 24 h after initiating HFNC was a good predictor of successful HFNC treatment.

The reviews of this paper are available via the supplemental material section.

Keywords: acute exacerbation, high-flow nasal cannula oxygen therapy, interstitial lung disease, predictive factor, pulse oximetric saturation to fraction of inspired oxygen

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Introduction

Interstitial lung disease (ILD), especially idiopathic pulmonary fibrosis (IPF), is a chronic progressive disease that induces fibrotic destruction of the lung parenchyma. An acute exacerbation (AE) of IPF can occur at any time during the clinical course and is significantly associated with mortality.[1,2] The in-hospital mortality rate in patients with AE-IPF is more than 50%,[3,4] especially in patients requiring invasive mechanical ventilation

(IMV), in whom it can reach 87%.[5] Based on these findings, the international guideline on managing IPF recommend against administering IMV to most patients with respiratory failure due to IPF.[1] Furthermore, AE of other types of ILD can also occur, such as idiopathic interstitial pneumonia (IIP) excluding IPF (non-IPF IIP), ILD associated with collagen tissue diseases (CTD-ILD), and chronic hypersensitivity pneumonitis (CHP). AE of these ILD types is fatal.[6–8]

High-flow nasal cannula (HFNC) oxygen therapy is a technique whereby heated and humidified oxygen is delivered to the nose at high flow rates, and has recently attracted attention as a new oxygen therapy for patients with hypoxemic respiratory failure. The rates of intubation and death under HFNC settings have been shown to be equivalent to those in patients undergoing conventional oxygen therapy and noninvasive positive-pressure ventilation (NPPV).[9–11] However, HFNC minimizes discomfort without decreasing quality of life.[12,13] Although it remains controversial whether HFNC is indicated for immunocompromised patients,[14,15] several studies have reported that HFNC was associated with lower risk for intubation compared with NPPV in those patients.[16,17] Patients with AE-ILD are usually treated with corticosteroids with or without immunosuppressive agents, which increase susceptibility to infections. Hence, HFNC may be a suitable oxygen delivery system for patients with acute hypoxemic respiratory failure due to AE-ILD. However, only limited evidence exists regarding the efficacy and tolerability of HFNC in patients with AE-ILD, and the possibility of delayed intubation leading to poor prognosis exists in this setting.[18] Furthermore, early predictors of the successful HFNC treatment in these patients remain to be elucidated.

In the current study, we evaluated HFNC treatment in patients with AE-ILD to assess the efficacy and tolerability of this treatment and sought to identify early predictive factors of successful HFNC treatment outcomes. To the best of our knowledge, this is the first study to show these predictive factors for HFNC outcomes in patients with AE-ILD.

Methods

Study design and data source

This was a double-center, retrospective, observational study at Seirei Mikatahara General Hospital and Hamamatsu University Hospital (Hamamatsu, Japan). All data were extracted from clinical records. The retrospective data analysis was approved by the ethics board of Seirei Mikatahara General Hospital (approval number: 17-05) and Hamamatsu University School of Medicine (approval number: 18-122), and this study was carried out in accordance with approved guidelines. The need for patient consent was waived because of the retrospective nature of the study; informed consent was based on the choice to opt out on the website.

Patients

The medical records of patients admitted to the Department of Respiratory Medicine from July 2013 to November 2017 were examined. The clinical records were reviewed, and patients were selected if they matched the following inclusion criteria: (1) a diagnosis of IPF, or non-IPF IIP, CTD-ILD, or CHP and (2) the use of HFNC for hypoxic respiratory failure associated with AE-ILD. For patients with IIP who did not undergo a pathological evaluation, we used the criteria of high-resolution computed tomography (HRCT) scanning patterns documented in the international guidelines.[19] Those who met the criteria for usual interstitial pneumonia (UIP) or probable UIP were defined as IPF, and those who met the criteria for indeterminate for UIP or alternative diagnosis were defined as non-IPF IIP. An experienced respiratory physician and a radiologist reviewed the HRCT films and evaluated the HRCT findings. AE-ILD was defined based on the criteria proposed by Collard and colleagues[20] and suggested by Leuschner and Behr,[21] with slight modifications as follows: (1) a previous or concurrent diagnosis of ILD; (2) acute worsening or development of dyspnea, typically <1 month in duration; (3) computed tomography with new bilateral ground-glass opacity or consolidation superimposed on a background pattern consistent with ILD; and (4) deterioration not fully explained by cardiac failure or fluid overload. We excluded patients who underwent IMV or NPPV before HFNC application. HFNC was delivered using the Optiflow® system, MR850 heated humidifier, RT202 delivery tube, and RT050/051 nasal cannula (Fisher & Paykel Healthcare, Auckland, New Zealand). The HFNC settings were determined by each attending physician.

Data collection

Clinical data and treatment before admission were obtained from the medical records. We also collected information on serum markers at AE-ILD diagnosis; presence of a do-not-intubate code; the partial pressure of arterial oxygen (PaO_2)/FIO_2 ratio upon initiating HFNC; SpO_2 and FIO_2 recorded at 0, 8, 24, and 48 h after initiating HFNC; and treatment regimens for AE-ILD. Adverse events associated with HFNC, interruptions or discontinuation of HFNC therapy at the patient's request, duration of HFNC use, and length of hospital stay were also investigated.

Outcome measures

The outcome measures were the success rates of HFNC, overall survival after initiating HFNC, temporary interruptions or discontinuation at the patient's request, and adverse events associated with HFNC. Successful HFNC treatment was defined as HFNC withdrawal with improved oxygenation, and other outcomes were defined as HFNC failure.

Statistical analysis

We summarized the patients' baseline characteristics using percentages for categorical variables and medians and interquartile ranges for continuous variables. The nonparametric Mann–Whitney *U* test was used to analyze continuous variables, and Fisher's exact test was used for categorical variables. Survival curves were plotted using the Kaplan–Meier method. The log-rank test was used to compare differences in survival. To assess the accuracy of different variables for correctly classifying patients who would succeed or fail on HFNC, receiver operating characteristic (ROC) curves were performed, and the areas under the ROC curve (AUROC) were calculated. The optimal cutoff point of continuous variables was chosen to maximize the sum of the sensitivity and specificity. Multivariate analysis was performed using logistic regression analysis to identify independent predictive factors for HFNC success or failure. Factors with a p value less than 0.10 in the univariable analyses were included in the multivariate model. A two-sided Student's t test was used to determine significant differences, and the significance level was defined as $p < 0.05$. All statistical analyses were performed using EZR, version 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[22]

Results

Patient characteristics and treatments for AE-ILD

During the study period, 66 patients with AE-ILD were treated with HFNC after receiving conventional oxygen therapy. The demographics of the study population are shown in Table 1. The patients comprised 51 men and 15 women with a median age of 78 years. Overall, 46 patients (69.7%) had a smoking history, and 17 patients (25.8%) used long-term oxygen therapy (LTOT) before admission. The numbers of ILD diagnoses were as follows: IPF, 31 (47.0%); non-IPF IIP, 22 (33.3%); CTD-ILD, 11 (16.7%); and CHP, 2 (3.0%). All patients received intravenous high-dose corticosteroids. In addition, immunosuppressive agents, azithromycin, and recombinant human soluble thrombomodulin were administered to 29 (43.9%), 29 (43.9%), and 17 (25.8%) patients, respectively. Polymyxin B-immobilized fiber column hemoperfusion was introduced in eight patients (12.1%). The median PaO_2/FIO_2 ratio at HFNC application was 115 (92–140). The median duration of HFNC therapy was 6 days. A total of 50 patients (75.8%) chose not to be intubated during hospitalization.

Outcomes and tolerability of HFNC

Of the 66 patients who received HFNC treatment, 26 (39.4%) successfully withdrew from HFNC with improved oxygenation. Of the 40 patients for whom HFNC treatment failed, 12 were switched to NPPV, two were switched to IMV, and 26 continued HFNC until death (Figure 1). Comparison of HFNC success and failure revealed no significant differences in the patients' age, sex, type of ILD, laboratory findings at AE-ILD diagnosis, or treatments for AE-ILD. Patients in the HFNC-success group had significantly less LTOT use before AE-ILD ($p = 0.045$) and longer hospital stays ($p < 0.001$) than those in the HFNC-failure group (Table 1). The 30-day survival rate from HFNC initiation was 48.5%, and Kaplan–Meier curves are shown in Figure 2(a). Although temporary interruption of HFNC was recorded in two patients, no patients felt discomfort or denied continuing HFNC. Adverse events related to HFNC were recognized in three patients: one had nasal bleeding, one had intraoral bleeding, and one had intraoral pain. No serious adverse events were observed in this study.

Table 1. Characteristics of patients with AE-ILD treated with HFNC.

Characteristics	All patients ($n=66$)	Outcome of HFNC treatment		p value
		Success ($n=26$)	Failure ($n=40$)	
Baseline characteristics				
Age, years	78 (73–82)	79 (74–82)	78 (72–82)	0.29
Sex, male	51 (77.3)	19 (73.1)	32 (80.0)	0.56
Smoking, current or former	46 (69.7)	18 (69.2)	28 (70.0)	>0.99
Type of ILD				0.19
IPF	31 (47.0)	9 (34.6)	22 (55.0)	
non-IPF	35 (53.0)	17 (65.4)	18 (45.0)	
LTOT, yes	17 (25.8)	3 (11.5)	14 (35.0)	0.045
Prednisolone before AE, yes	28 (42.4)	9 (34.6)	19 (47.5)	0.32
Pirfenidone or nintedanib, yes	8 (12.1)	1 (3.8)	7 (17.5)	0.13
Treatments of AE-ILD				
Intravenous high-dose corticosteroids, yes	66 (100)	26 (100)	40 (100)	>0.99
Immunosuppressant, yes	29 (43.9)	10 (38.5)	19 (47.5)	0.61
Azithromycin, yes	29 (43.9)	13 (50.0)	16 (40.0)	0.46
rhTM, yes	17 (25.8)	6 (23.1)	11 (27.5)	0.78
PMX, yes	8 (12.1)	3 (11.5)	5 (12.5)	>0.99
At HFNC application				
P/F ratio, Torr	115 (92–140)	130 (95–157)	109 (86–127)	0.098
Flow of HFNC, l/min	40 (40–45)	40 (40–45)	40 (40–45)	0.97
Clinical course				
DNI code, yes	50 (75.8)	17 (65.4)	33 (82.5)	0.15
Length of hospital stay, days	43 (18–70)	60 (47–73)	26 (10–42)	<0.001
Duration of HFNC use, days	6 (3–16)	7 (4–14)	6 (2–17)	0.36

Each parameter is expressed as number (percentage) or median (interquartile range). Parameters in each group were compared using Fisher's exact test or the Mann–Whitney *U* test.
AE, acute exacerbation; DNI, do-not-intubate; HFNC, high-flow nasal cannula oxygen therapy; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LTOT, long-term oxygen therapy; P/F, partial pressure of arterial oxygen/fraction of inspired oxygen; PMX, polymyxin B-immobilized fiber column hemoperfusion; rhTM, recombinant human soluble thrombomodulin.

Impact of SpO_2/FIO_2 ratio on HFNC treatment outcome

Table 2 shows the transitions of SpO_2 and FIO_2 and the SpO_2/FIO_2 ratio. Significant differences in FIO_2 and the SpO_2/FIO_2 ratio appeared from 8 h after initiating HFNC between the HFNC-success and HFNC-failure groups. The differences became more apparent at 24 h after initiation.

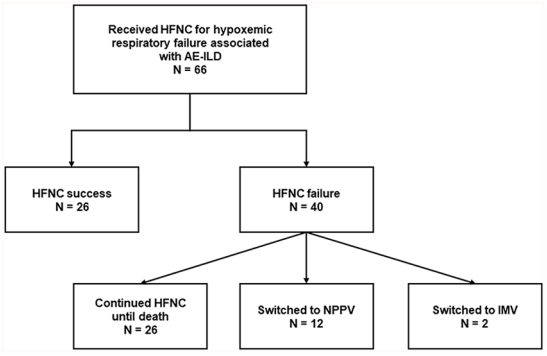

Figure 1. Diagram of patient flow in this study.
AE-ILD, acute exacerbation of interstitial lung disease; HFNC, high-flow nasal cannula oxygen therapy; IMV, invasive mechanical ventilation; NPPV, noninvasive positive-pressure ventilation.

Figure 3 shows the changes in the SpO_2/FIO_2 ratio for each patient with HFNC success and failure, respectively. Their accuracies in predicting the HFNC treatment outcomes were assessed by calculating the AUROC (Table 3). No variables analyzed at 0 or 8 h after HFNC initiation had good predictive capacities for the outcome (AUROC < 0.7). The AUROC of the SpO_2/FIO_2 ratio reached good predictive accuracy (AUROC of 0.802) at 24 h after HFNC initiation, and this continued at 48 h. When the cutoff point was set at 170.9 to maximize the sum of the sensitivity and specificity, the SpO_2/FIO_2 ratio at 24 h showed 96.2% sensitivity and 68.4% specificity.

Univariate and multivariate analyses of predictive factors for HFNC outcome

In the univariate analysis, LTOT use [odds ratio (OR), 0.24; 95% confidence interval (CI), 0.06–0.95; $p = 0.042$] and an SpO_2/FIO_2 ratio $\geqslant$170.9 after 24 h (OR, 58.3; 95% CI, 7.07–481.00; $p < 0.001$] were significant predictive factors for the HFNC outcome (Table 4). The HFNC outcome was independently associated with the SpO_2/FIO_2 ratio after 24 h based on the multivariate logistic regression analysis, including the SpO_2/FIO_2 ratio and LTOT use (OR, 51.3; 95% CI, 6.13–430.00; $p < 0.001$) (Table 4). Overall survival from the time of HFNC initiation was significantly better in patients with an SpO_2/FIO_2 ratio of $\geqslant$170.9 after 24 h of initiating HFNC than in those with an SpO_2/FIO_2 ratio of $<$170.9 (30-day survival rate: 70.3% *versus* 20.7%, $p < 0.001$) [Figure 2(b)].

Discussion

The current study was conducted to evaluate the efficacy and tolerability of HFNC in patients with AE-ILD. Our results showed that HFNC was well tolerated in these patients, and approximately 40% of patients showed improved oxygenation and were able to successfully withdraw from HFNC. Furthermore, the SpO_2/FIO_2 ratio at 24 h after HFNC initiation was a significant predictor of successful HFNC treatment.

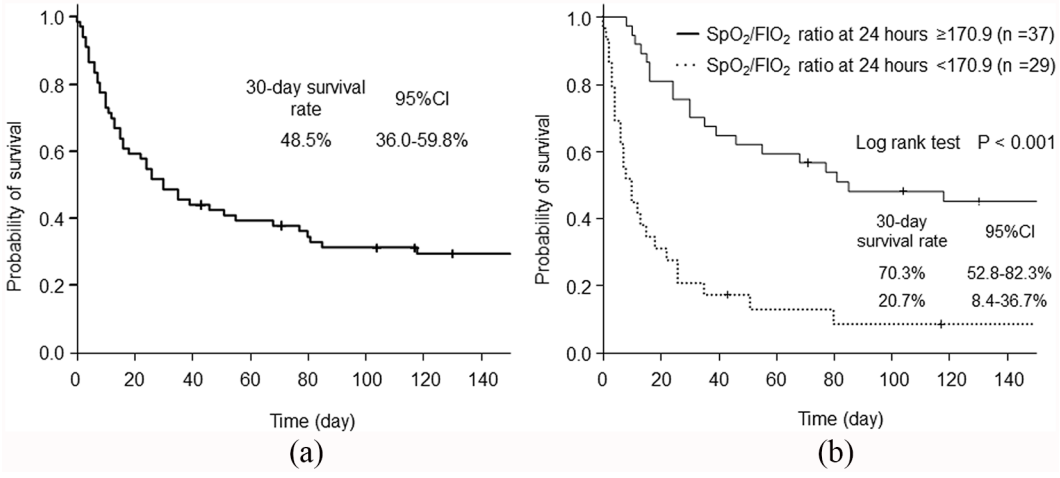

Figure 2. (a) Kaplan–Meier survival curve for patients with acute exacerbation of interstitial lung disease treated with high-flow nasal cannula oxygen therapy. (b) Stratification according to the SpO_2/FiO_2 ratio 24 h after initiating high-flow nasal cannula oxygen therapy.
SpO_2/FiO_2, pulse oximetric saturation to fraction of inspired oxygen; CI, confidence interval.

Table 2. Changes in respiratory variables during HFNC.

Variable	Time	HFNC success	HFNC failure	*p* value
SpO_2	0 h	94 (93–95)	94 (93–96)	0.73
	8 h	95 (92–96)	94 (93–95)	0.70
	24 h	95 (93–96)	93 (91–96)	0.22
	48 h	96 (94–96)	94 (92–95)	0.027
FIO_2	0 h	0.58 (0.50–0.68)	0.60 (0.50–0.80)	0.34
	8 h	0.50 (0.45–0.55)	0.60 (0.50–0.80)	0.007
	24 h	0.43 (0.40–0.50)	0.68 (0.50–0.80)	<0.001
	48 h	0.38 (0.35–0.40)	0.75 (0.50–1.00)	<0.001
SpO_2/FIO_2	0 h	165 (140–190)	161 (117–189)	0.35
	8 h	186 (166–216)	153 (121–187)	0.007
	24 h	216 (190–242)	141 (115–188)	<0.001
	48 h	253 (235–276)	123 (99–184)	<0.001

Each parameter is expressed as median (interquartile range). Parameters in each group were compared using the Mann–Whitney *U* test.
FIO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula oxygen therapy; SpO_2, pulse oximetric saturation.

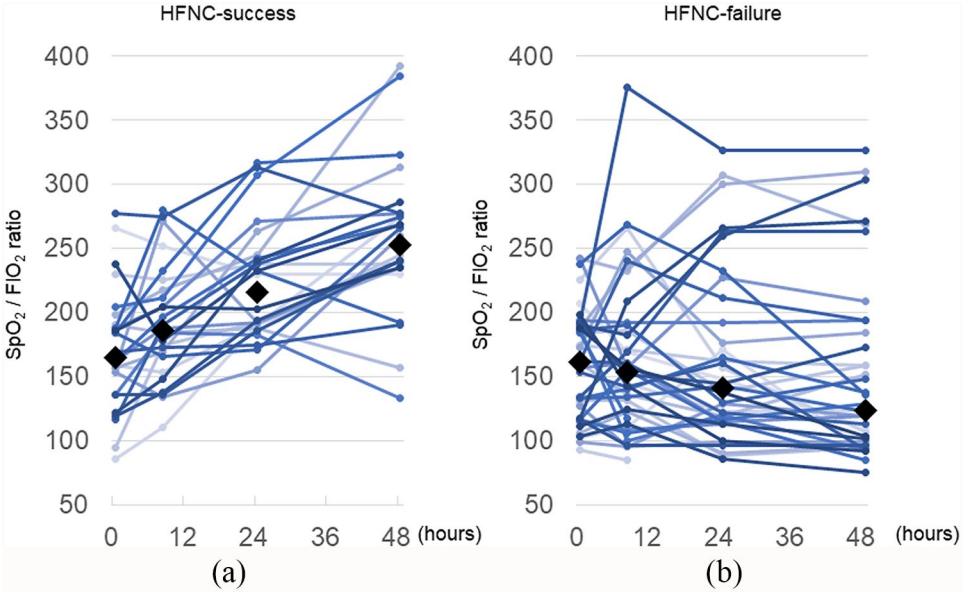

Figure 3. Changes in the SpO_2/FiO_2 ratio for each patient with HFNC (a) success and (b) failure. Diamond marks (♦) indicate the median.
SpO_2/FiO_2, pulse oximetric saturation to fraction of inspired oxygen; HFNC, high-flow nasal cannula oxygen therapy.

Table 3. Decision accuracy of the outcome of high-flow nasal cannula oxygen therapy.

	Variable	AUROC	95% CI
0 h	FIO_2	0.569	0.428–0.711
	SpO_2/FIO_2	0.568	0.426–0.711
8 h	FIO_2	0.695	0.568–0.822
	SpO_2/FIO_2	0.698	0.571–0.825
24 h	FIO_2	0.792	0.677–0.907
	SpO_2/FiO_2	0.802	0.689–0.914
48 h	FIO_2	0.851	0.752–0.950
	SpO_2/FIO_2	0.856	0.759–0.952

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; FIO_2, fraction of inspired oxygen; SpO_2, pulse oximetric saturation.

HFNC provides sufficiently heated and humidified oxygen to relieve nasal cavity irritation.[23] Therefore, this treatment minimizes discomfort and is well tolerated by patients. In patients with AE-ILD who are usually treated with strong immunosuppressive therapy, IMV has increased risks of pneumonia such as ventilator-associated lung injury and pneumothorax.[24] There is a possibility that HFNC contributes to oral care and mucociliary clearance owing to appropriate heating and humidification without oral obstructive devices such as an intubation tube.[25] Furthermore, HFNC reduces the risk of barotrauma such as pneumothorax.[26] Intubation rates are reportedly lower in immunocompromised patients with acute respiratory failure treated by HFNC than in those treated by NPPV.[16,17] Therefore, HFNC therapy in patients with AE-ILD is expected to lead to maintain quality of life and decreased complication rates associated with ventilation.

NPPV, which is another respiratory management technique for patients with AE-ILD, has been frequently used in such cases during the last decade. Several retrospective studies have analyzed the effectiveness of NPPV in patients who have ILD with acute hypoxemic respiratory failure. The reported 30-day survival rate of patients treated with NPPV ranges from 26.3% to 68.4%.[27] However, patients often refuse NPPV because they fear discomfort associated with wearing an NPPV mask. Mollica and colleagues[28] reported that 3 of 18 patients who had IPF with acute respiratory failure discontinued NPPV at the patient's request. Conversely, in the current study, no discontinuations at the patient's request occurred under HFNC use. Moreover, we recently reported that HFNC had a survival rate similar to that of NPPV as well as high tolerability in patients with ILD who had do-not-intubate orders.[29] These results suggest that HFNC is an effective alternative to NPPV in these patients.

Ito and colleagues[30] examined patients with AE-ILD and reported that HFNC reduced the use of sedoanalgesia and the number of patients who discontinued oral intake. Vianello and colleagues[31] suggested that HFNC should be applied to patients who do not respond to conventional oxygen therapy. However, the number of patients who do not show improvement in oxygenation is not small even after treatment with HFNC, and unduly delaying intubation may increase mortality, as reported for patients undergoing NPPV.[18,32] Therefore, an accurate predictor needs to be identified to determine which patients should be maintained under HFNC and which should be switched to NPPV or IMV. Furthermore, induction of palliative care should be considered when HFNC fails. In clinical practice, the SpO_2/FIO_2 ratio can be used as a noninvasive indicator of oxygenation.[33] This ratio correlates with the PaO_2/FIO_2 ratio,[34] and recent studies have shown that the SpO_2/FIO_2 ratio is a good predictor of HFNC treatment.[35,36] In the current study, an SpO_2/FiO_2 ratio $\geqslant$170.9 at 24 h after initiation of HFNC was a significant predictor of successful HFNC treatment. AUROC of SpO_2/FiO_2 ratio at 48 h was better than that at 24 h (0.856 and 0.802, respectively). Kang and colleagues reported that overall mortality was better in patients intubated within 48 h after initiation of HFNC.[18] Therefore, SpO_2/FiO_2 ratio at 48 h has a great risk of delayed intubation, and decision-making at 24 h is better tolerated and more preferable than that at 48 h. Further, AUROC of SpO_2/FiO_2 ratio at 24 h was more than 0.8 and reliable. Therefore, we decided to use the values at 24 h after HFNC initiation.

Upon failure of HFNC treatment, the attending doctor should carefully analyze each patient before deciding whether to continue HFNC or switch to NPPV/IMV, although IMV may be a reasonable intervention for only a minority of patients with ILD, and the international guidelines on managing

Table 4. Univariate and multivariate analyses of predictive factors for successful HFNC.

	Odds ratio	95% CI	*p* value
Univariate analysis of predictive factors of the outcome of HFNC			
Age, years	1.04	0.97–1.12	0.24
Sex, male	0.68	0.21–2.17	0.51
Smoking, current or former	0.96	0.33–2.82	0.95
Type of ILD, non-IPF	2.31	0.83–6.40	0.11
LTOT, yes	0.24	0.06–0.95	0.042
Prednisolone before AE, yes	0.59	0.21–1.62	0.30
Pirfenidone or nintedanib, yes	0.19	0.02–1.63	0.13
Etiology of AE-ILD, triggered	1.12	0.43–3.13	0.77
WBC, ×100/μl	1.00	0.99–1.01	0.99
CRP, mg/dl	1.03	0.95–1.12	0.47
LDH, ×10 U/l	0.99	0.96–1.02	0.44
KL-6, ×100 U/ml	0.97	0.92–1.01	0.17
SP-D, ×10 ng/ml	1.00	0.99–1.02	0.54
P/F ratio at HFNC application, ×10 Torr	1.08	0.94–1.23	0.27
Immunosuppressant, yes	0.69	0.25–1.89	0.47
Azithromycin, yes	1.50	0.55–4.06	0.43
rhTM, yes	0.79	0.25–2.49	0.69
PMX, yes	0.91	0.20–4.20	0.91
24-h $SpO_2/FiO_2 \geqslant 170.9$, yes	58.3	7.07–481	<0.001
Multivariate analysis of predictive factors of the outcome of HFNC			
LTOT, yes	0.52	0.09–3.04	0.47
24 h $SpO_2/FIO_2 \geqslant 170.9$, yes	51.3	6.13–430	<0.001

AE, acute exacerbation; CI, confidence interval; CRP, C-reactive protein; FIO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula oxygen therapy; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; P/F, partial pressure of arterial oxygen/fraction of inspiratory oxygen; PMX, polymyxin B-immobilized fiber column hemoperfusion; rhTM, recombinant human soluble thrombomodulin; SP-D, surfactant protein-D; SpO_2, pulse oximetric saturation; WBC, white blood cell.

IPF make a weak recommendation against using IMV.[1] We recently reported the usefulness of HFNC in patients with ILD with do-not-intubate orders. In that study, HFNC was more tolerated than NPPV and allowed patients to eat and converse until just before death.[29] In patients who decide not to be intubated, continuing HFNC therapy may be a reasonable respiratory management technique in terms of palliative care.

This study had some mentionable limitations. First, this study was retrospectively conducted. Second, only a small number of patients with AE-ILD were analyzed due to its rarity. The

incidence of IPF, which is the most frequent cause of AE, is 3–9 cases/100,000/years.[37] Further, the incidence of AE-IPF was 8.6%/year,[38] and AE of CTD-ILD was 1.25%/year.[7] A multicenter study should be performed. Third, this study could not compare other respiratory management systems such as NPPV, IMV, or conventional oxygen therapy. Future studies are needed to elucidate the best respiratory management system for AE-ILD. Fourth, the ROX index (the ratio of SpO_2/FiO_2 to respiratory rate) was not evaluated because we have no complete data of respiratory rate in the present study. However, Roca and colleagues reported that among components of the ROX index, SpO_2/FiO_2 had a greater weight than respiratory rate, and SpO_2/FiO_2 had a good predictive capacity 24 h after HFNC initiation equivalent to the ROX index.[39]

In conclusion, HFNC was well tolerated in patients with hypoxemic respiratory failure associated with AE-ILD, and HFNC was successfully withdrawn in approximately 40% of patients with AE-ILD. Additionally, the SpO_2/FIO_2 ratio 24 h after HFNC initiation was a significant predictor of successful HFNC treatment. HFNC may be a reasonable treatment in these patients, although further study is required to validate our findings.

Author contributions

The author contributions were as follows: T.K: study conception and design, data collection, data analysis and interpretation, and manuscript writing. H.Y: study conception and design, data analysis and interpretation, manuscript writing, and final approval of manuscript. N.E: data analysis and interpretation, manuscript writing, and final approval of manuscript. H.H., H.H., Y.S., M.K., K.F., T.F., Y.N., and N.I: data collection and data analysis and interpretation. K.Y: study conception and design, data collection, and data analysis and interpretation. T.S: manuscript writing, final approval of manuscript, and administrative support.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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