Original Article

Comparison of high-flow nasal cannula oxygen therapy and non-invasive ventilation as first-line therapy in respiratory failure: a multicenter retrospective study

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Aim: To identify which subgroups of respiratory failure could benefit more from high-flow nasal cannula oxygen therapy (HFNC) or non-invasive ventilation (NIV).

Methods: We undertook a multicenter retrospective study of patients with acute respiratory failure (ARF) who received HFNC or NIV as first-line respiratory support between January 2012 and December 2017. The adjusted odds ratios (OR) with 95% confidence intervals (CI) for HFNC versus NIV were calculated for treatment failure and 30-day mortality in the overall cohort and in patient subgroups.

Results: High-flow nasal cannula oxygen therapy and NIV were used in 200 and 378 patients, and the treatment failure and 30-day mortality rates were 56% and 34% in the HFNC group and 41% and 39% in the NIV group, respectively. The risks of treatment failure and 30-day mortality were not significantly different between the two groups. In subgroup analyses, HFNC was associated with increased risk of treatment failure in patients with cardiogenic pulmonary edema (adjusted OR 6.26; 95% CI, 2.19–17.87; $P < 0.01$) and hypercapnia (adjusted OR 3.70; 95% CI, 1.34–10.25; $P = 0.01$), but the 30-day mortality was not significantly different in these subgroups. High-flow nasal cannula oxygen therapy was associated with lower risk of 30-day mortality in patients with pneumonia (adjusted OR 0.43; 95% CI, 0.19–0.94; $P = 0.03$) and in patients without hypercapnia (adjusted OR 0.51; 95% CI, 0.30–0.88; $P = 0.02$).

Conclusion: High-flow nasal cannula oxygen therapy could be more beneficial than NIV in patients with pneumonia or non-hypercapnia, but not in patients with cardiogenic pulmonary edema or hypercapnia.

Key words: Cardiogenic pulmonary edema, high-flow nasal cannula oxygen therapy, hypercapnia, non-invasive ventilation, pneumonia

INTRODUCTION

ACUTE RESPIRATORY FAILURE (ARF) is a common complication in hospitalized patients. The causes of ARF include pneumonia, cardiogenic pulmonary edema (CPE), and chronic obstructive pulmonary disease (COPD). Although oxygen therapy using conventional devices is usually prescribed for patients with ARF, many patients require advanced respiratory support. Invasive mechanical ventilation (IMV) is traditionally used in such patients. However, with recent recognition of ventilator-associated adverse events, alternatives to IMV for providing respiratory support are desired.

In the past few decades, non-invasive ventilation (NIV) has emerged as a primary alternative to IMV, and the use of NIV for ARF has increased over time.[1] This increased use is mainly due to its use in patients with highly evident etiologies, such as CPE or COPD exacerbations. However, the use of NIV has decreased in patients with de novo ARF, types of ARF without cardiogenic origin or preexisting

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chronic lung disease, because of the limited success of NIV in these patients.

High-flow nasal cannula oxygen therapy (HFNC) is an alternative to IMV that was recently introduced to treat ARF. It provides some physiological effects, such as some extent of expiratory positive airway pressure (EPAP)[2] and a washout effect on CO_2 in the upper airway.[3] A previous study showed that HFNC could decrease the need for positive airway ventilation, including NIV.[4] In addition, a randomized control trial revealed that the 90-day mortality rate was lower with HFNC than with NIV in patients with de novo ARF.[5] This suggests that HFNC might be more beneficial than NIV if used in appropriate patients. However, there is limited evidence supporting the use of HFNC to treat etiologies for which NIV is well established, and NIV could be more appropriate than HFNC in these patients.

We undertook a retrospective study to identify which subgroups of patients might benefit most from HFNC or NIV.

METHODS

Study setting and population

WE UNDERTOOK A multicenter retrospective analysis of patients admitted to one teaching hospital and three general hospitals in Japan. The study was approved by the institutional review board in each institution. We retrieved the medical records of all adult patients (≥18 years old) with an estimated P_aO_2/F_IO_2 (P/F) ratio of <300 who received HFNC (HFNC group) or NIV (NIV group) as first-line respiratory support between January 2012 and December 2017. Patients were excluded if they had chronic respiratory failure without acute exacerbation, received home-based NIV, their respiratory support was suspended for surgery or invasive procedures, or data were incomplete. There were no established protocols for the use of alternative respiratory support or intubation in any of the institutions; the choice of respiratory support was made by the attending physician. The NIV group included patients who received either non-invasive continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP). Dedicated NIV ventilators (BiPAP vision or Respironics V60 ventilator; Philips Respironics, Murrysville, PA, USA) and a full-face mask were used for NIV. The Nasal High Flow system (Fisher & Paykel Healthcare, Auckland, New Zealand) was used for HFNC.

Data collection

We collected the following baseline data: age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, cause of respiratory failure, and extrapulmonary Sequential Organ Failure Assessment (SOFA) score (excluding respiratory variables) at the start of alternative respiratory support. We also retrieved physiological data immediately before and arterial blood gas analysis within 6 h before alternative respiratory support was started. The primary outcome was failure of alternative respiratory support (treatment failure), and the secondary outcome was 30-day mortality. Treatment failure was defined as composite outcome including: (i) intubation, (ii) switching to another treatment without improvement, or (iii) death during HFNC or NIV.

Statistical analysis

The clinical data and outcomes were compared between the HFNC and NIV groups. In addition, the adjusted odds ratios (OR) with 95% confidence intervals (CI) for HFNC versus NIV were calculated for treatment failure and 30-day mortality.

Variables are shown as the median (interquartile range) or number (percentage) of patients. Univariate analyses were carried out using the χ^2-test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Multivariable logistic regression analyses were carried out to determine the adjusted ORs. The regression analyses were adjusted for age, cause of respiratory failure, respiratory rate at the start of respiratory support, P/F ratio, P_aCO_2, APACHE II score, and extrapulmonary SOFA score. These analyses were undertaken in the overall cohort and in subgroups of patients. The interaction between the type of respiratory support and subgroups was evaluated by adding interacted items of them to above regression models. In all tests, two-tailed *P*-values of <0.05 were considered statistically significant. We used IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA) for all statistical analyses.

RESULTS

DURING THE STUDY period, 210 and 426 patients with respiratory failure received HFNC and NIV, respectively (Fig. 1). After applying exclusion criteria, we analyzed data for 200 patients in the HFNC group and 378 patients in the NIV group.

The baseline demographic characteristics of the patients in each group are presented in Table 1. The HFNC group was significantly younger than the NIV group. Respiratory rate, APACHE II score, and extrapulmonary SOFA score were significantly lower in the HFNC group than in the NIV group. Although the P/F ratio tended to be lower in the HFNC group, P_aCO_2 levels were significantly higher in the

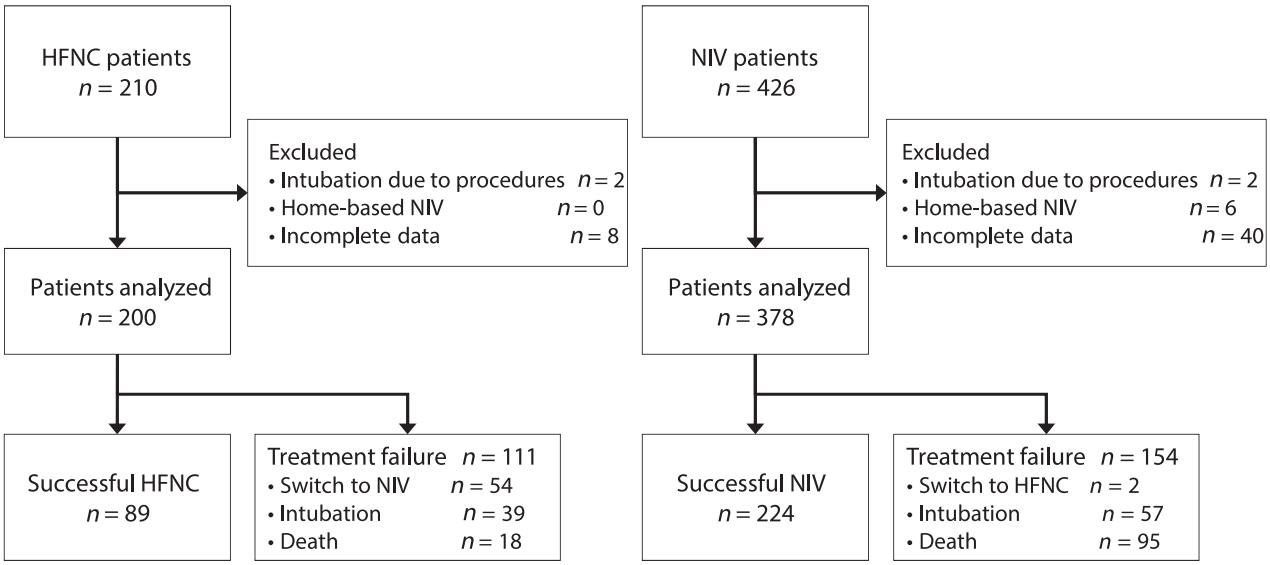

Fig. 1. Flowchart of the present study included patients with respiratory failure who received high-flow nasal cannula oxygen therapy (HFNC) or non-invasive ventilation (NIV) as first-line therapy between January 2012 and December 2017.

NIV group. Non-invasive ventilation was started in the CPAP mode in 171 patients (45%) and 232 patients (61%) underwent BPAP.

The outcomes of patients for the overall cohort and in each subgroup are shown in Table 2. In the univariate analyses of all patients, although the treatment failure rate was greater in the HFNC group than in the NIV group (56% versus 41%, $P = 0.001$), the 30-day mortality rate was not significantly different between the two groups (29% versus 32%, $P = 0.456$). Of 111 patients with treatment failure in the HFNC group, 54 (49%) were switched to NIV, and 20 (37%) of these patients were successfully treated with NIV. In contrast, two patients were switched from NIV to HFNC, and both were intubated after the switch. Although the most common reason for treatment failure was persistent hypoxia in the HFNC and NIV groups (74% versus 53%), treatment failure due to hypercapnia (14% versus 24%) or circulatory instability (8% versus 16%) was less frequent in the HFNC group. In the subgroup analyses, treatment failure was more common in the HFNC group than in the NIV group in patients with CPE, mild to moderate hypoxia, or hypercapnia. Among patients with pneumonia, although the treatment failure rate was not significantly different between the two groups, the 30-day mortality rate was significantly lower in the HFNC group (28% versus 56%, $P = 0.001$).

The adjusted ORs for treatment failure and 30-day mortality are shown in Figures 2 and 3, respectively. Overall, HFNC was not significantly associated with increased risks of treatment failure or 30-day mortality. In the subgroup analyses, HFNC was associated with increased risk of treatment failure compared with NIV in patients with CPE (adjusted OR 6.26; 95% CI, 2.19–17.87; $P = 0.001$) or hypercapnia (adjusted OR 3.70; 95% CI, 1.34–10.25; $P = 0.012$). However, HFNC was not associated with increased risk of 30-day mortality in these subgroups. Although HFNC was not significantly associated with decreased risk of treatment failure in patients with pneumonia or patients without hypercapnia, HFNC was associated with significantly decreased risk of 30-day mortality in patients with pneumonia (adjusted OR 0.43; 95% CI, 0.19–0.94; $P = 0.014$) and in patients without hypercapnia (adjusted OR 0.51; 95% CI, 0.30–0.88; $P = 0.015$). The significant interactive effects on treatment failure and 30-day mortality were shown between the respiratory support and cause of respiratory failure, and the presence of hypercapnia.

DISCUSSION

IN THE PRESENT study, we compared the effectiveness of HFNC and NIV overall and in various subgroups of patients. We found that the risk of treatment failure was increased in patients with CPE and hypercapnia who received HFNC. However, HFNC was associated with lower risk of 30-day mortality in patients with pneumonia and patients without hypercapnia.

The usefulness of HFNC has been investigated in recent studies, which generally compared HFNC with conventional

Table 1. Background characteristics of patients treated with high-flow nasal cannula oxygen therapy (HFNC) or non-invasive ventilation (NIV)

	HFNC(n = 200)	NIV(n = 378)	P-value
Age, years	74 (66–82)	78 (69–84)	0.020
Gender, male	127 (64)	231 (61)	0.574
Cause of respiratory failure			<0.001
Pneumonia	64 (32)	88 (23)	
Intestinal lung disease	38 (19)	53 (14)	
Extrapulmonary ARDS[†]	30 (15)	20 (5)	
Cardiogenic pulmonary edema	24 (12)	166 (44)	
Exacerbation of CLD	3 (2)	24 (6)	
Others	41 (21)	27 (7)	
De novo ARF	163 (82)	161 (43)	<0.001
Immunocompromised	44 (22)	73 (19)	0.444
Respiratory parameters on treatment start			
Respiratory rate, /min	26 (22–31)	29 (24–34)	<0.001
P/F ratio[‡]	144 (116–182)	156 (116–210)	0.062
Severe hypoxia (P/F ≤ 100)	20 (10)	57 (15)	0.087
Mild to moderate hypoxia	180 (90)	321 (85)	
P_aCO_2, Torr	36 (32–41)	41 (33–58)	<0.001
Hypercapnia	30 (15)	156 (41)	<0.001
pH	7.43 (7.38–7.47)	7.34 (7.24–7.45)	<0.001
APACHE II score	15 (11–19)	18 (14–23)	<0.001
Extrapulmonary SOFA score	2 (1–4)	3 (1–5)	0.008
Initial setting			
F_IO_2	0.80 (0.60–1.00)	0.60 (0.50–0.80)	<0.001
Flow, L/min	40 (40–40)		
EPAP, cmH_2O		6 (4–8)	

Values are shown as number (percentage) of patients or median (interquartile range).
[†]Extrapulmonary acute respiratory distress syndrome (ARDS) was diagnosed if patients with extrapulmonary origin fulfilled all criteria of the Berlin definition except positive end-expiratory pressure level.
[‡]F_IO_2 during conventional oxygen therapy was estimated as: (oxygen flow L/min) × 0.03 + 0.21.[5]
APACHE II, Acute Physiology and Chronic Health Evaluation II; ARF, acute respiratory failure; CLD, chronic lung disease; EPAP, expiratory positive airway pressure; P/F, P_aO_2/F_IO_2; SOFA, Sequential Organ Failure Assessment.

oxygen therapy; a small number of studies have compared HFNC and NIV, largely in patients after surgery or extubation. In addition, because many of the studies included heterogeneous patients, it is unclear whether HFNC is more or less effective than NIV in some groups of patients.

Cardiogenic pulmonary edema is a well-established indication for NIV. In patients with CPE, NIV was associated with lower intubation and mortality rates compared with conventional oxygen therapy.[6] In contrast, there is limited evidence supporting the effectiveness of HFNC in CPE. One randomized control study in patients with CPE showed that HFNC decreased the respiratory rate, but the rate of step-up to advanced respiratory support did not differ between HFNC and conventional oxygen therapy.[7] However, that study had insufficient power to evaluate the rate of treatment failure with HFNC because of its low severity and small number of patients. In CPE patients treated with NIV, the positive airway pressure is expected to play key roles in improving respiratory and hemodynamic status.[8] Although the optimal positive airway pressure in patients with CPE is unclear, an EPAP of 7.5–11 cmH_2O in CPAP and 4–11 cmH_2O in BPAP was used in a study that showed the benefit of NIV in CPE.[6] A previous study showed that HFNC could not provide a similar EPAP.[2] This insufficient EPAP could explain the increased risk of treatment failure of HFNC in patients with CPE.

Patients with hypercapnic respiratory failure are also frequently treated with NIV, especially patients with COPD exacerbation or CPE. In addition to pressure support in BPAP, the improved respiratory mechanics provided by

Table 2. Outcomes of high-flow nasal cannula oxygen therapy (HFNC) or non-invasive ventilation (NIV) in the overall patient cohort and in subgroups of patients

	Treatment failure			30-day mortality		
	Event/total (%)		*P*-value	Event/total (%)		*P*-value
	HFNC	NIV		HFNC	NIV	
Overall	111/200 (56)	154/378 (41)	0.001	58/200 (29)	121/378 (32)	0.456
Cause of respiratory failure						
Pneumonia	37/64 (58)	60/88 (68)	0.189	18/64 (28)	49/88 (56)	0.001
Intestinal lung disease	22/38 (58)	39/53 (74)	0.116	18/38 (47)	34/53 (64)	0.111
Cardiogenic pulmonary edema	11/24 (46)	20/166 (12)	<0.001	3/24 (13)	16/166 (10)	0.662
Immunocompromised	25/44 (57)	48/73 (66)	0.334	17/44 (39)	36/73 (49)	0.261
Hypoxia						
Mild to moderate	95/180 (53)	117/321 (36)	<0.001	47/180 (26)	94/321 (29)	0.449
Severe	16/20 (80)	37/57 (65)	0.210	11/20 (55)	27/57 (47)	0.557
Hypercapnia						
Yes	20/30 (67)	55/156 (35)	0.001	10/30 (33)	39/156 (25)	0.343
No	91/170 (54)	99/222 (45)	0.079	48/170 (28)	82/222 (37)	0.070

Values are expressed as the number of events/total (percentage).

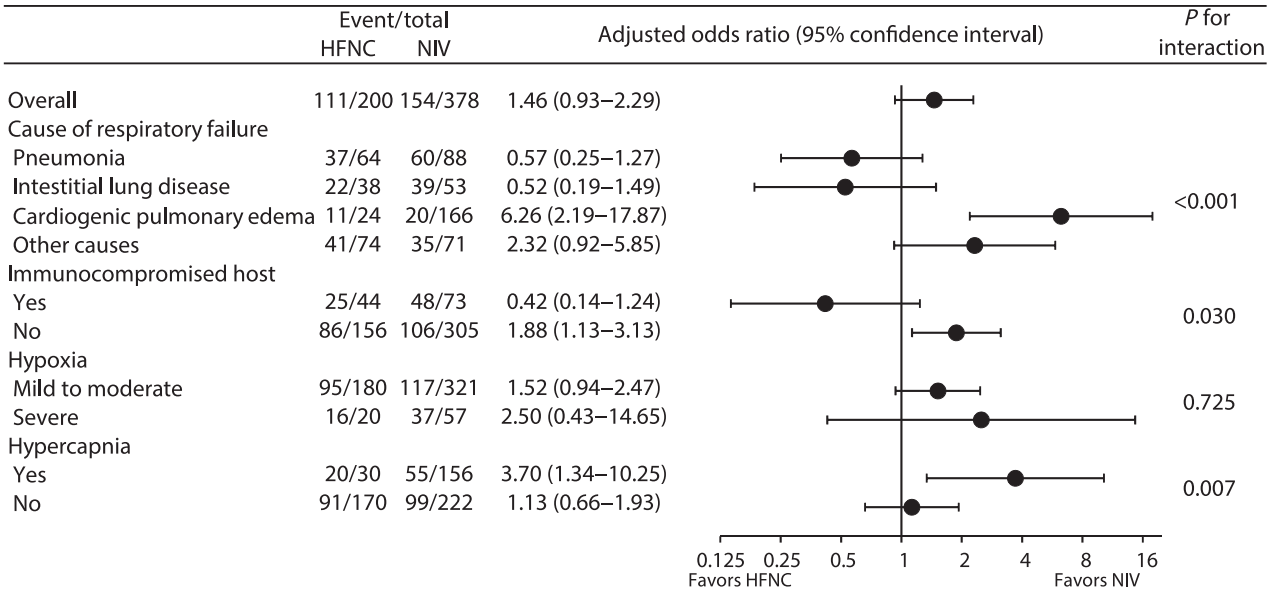

Fig. 2. Risk of treatment failure with high-flow nasal cannula oxygen therapy (HFNC) versus non-invasive ventilation (NIV). Other causes of respiratory failure included extrapulmonary acute respiratory distress syndrome and exacerbation of chronic lung disease. Variables used for the adjustment included age, cause of respiratory failure, respiratory rate at the start of respiratory support, P_aO_2/F_IO_2 ratio, P_aCO_2, Acute Physiology and Chronic Health Evaluation II score on admission, and extrapulmonary Sequential Organ Failure Assessment score (excluding respiratory variables).

EPAP can improve ventilation and reduce P_aCO_2.[9] Although HFNC can also reduce P_aCO_2 through a washout effect on the upper airway,[3] there is limited evidence for the effectiveness of HFNC in hypercapnic patients. Lee *et al.*[10] reported comparable effects of HFNC and NIV on the prevention of intubation and mortality rate in patients with

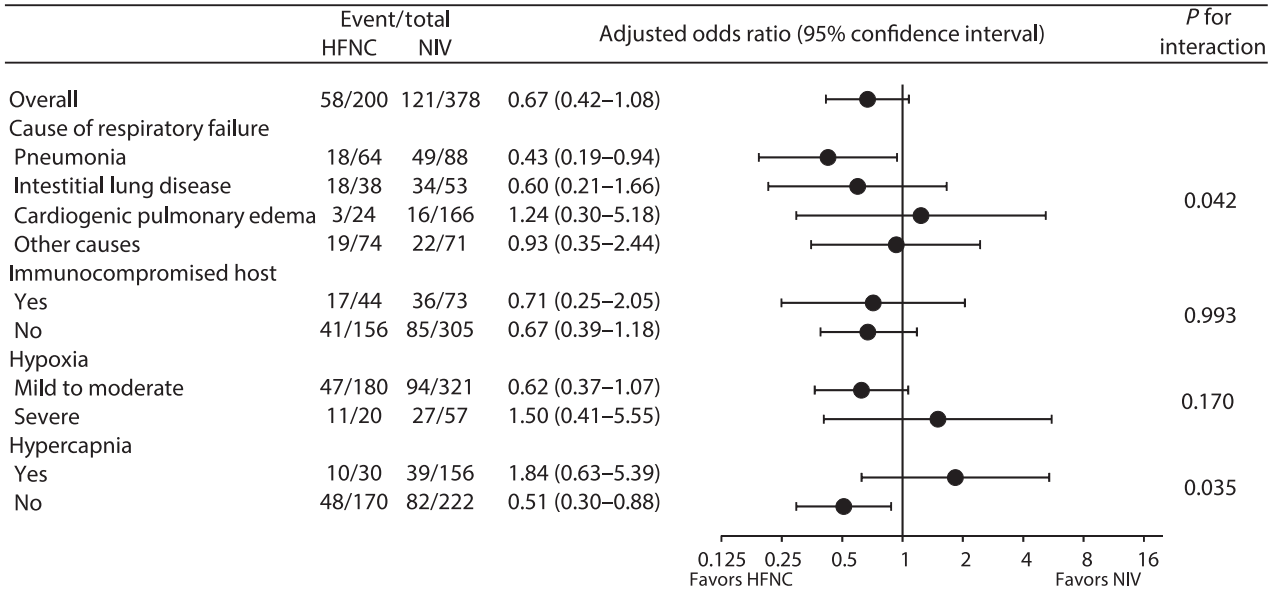

Fig. 3. Risk of 30-day mortality with high-flow nasal cannula oxygen therapy (HFNC) versus non-invasive ventilation (NIV). Other causes of respiratory failure included extrapulmonary acute respiratory distress syndrome and exacerbation of chronic lung disease. Variables used for the adjustment included age, cause of respiratory failure, respiratory rate at the start of respiratory support, P_aO_2/F_IO_2 ratio, P_aCO_2, Acute Physiology and Chronic Health Evaluation II score on admission and extrapulmonary Sequential Organ Failure Assessment score (excluding respiratory variables).

hypercapnia due to COPD exacerbation. Unfortunately, the present study included few patients with COPD exacerbation, which could explain our inconsistent results. Because prior studies reported that the risk of treatment failure was lower in patients with hypercapnic COPD exacerbation than in hypercapnic patients without COPD placed on NIV[11] and HFNC,[12] patients with hypercapnic COPD exacerbation can be treated with either type of respiratory support, whereas NIV may be more suitable than HFNC for patients with other causes of hypercapnia.

Hypoxic de novo ARF is a common indication for respiratory support and is frequently caused by pneumonia, like in the patients included in the present study. In this situation, one randomized control study reported that the mortality rate was lower with HFNC than with NIV, although the rate of treatment failure was not significantly different.[5] These results are consistent with our own. One possible reason for the higher mortality rate in NIV is the increased risk of volutrauma. The harmful effect of a high tidal volume was recently recognized, even during NIV[13] or spontaneous breathing.[14] In patients with de novo ARF, NIV could increase the tidal volume,[15] and low tidal volume ventilation was achieved in just one-quarter of patients.[13] High-flow nasal cannula oxygen therapy was reported to decrease the work of breathing and minute ventilation without increasing tidal volume, probably due to its washout effect on the upper airway.[16] Therefore, HFNC might be associated with less risk of aggravating lung injury due to excessive lung expansion, as compared with NIV. Another possible reason is that both approaches have different effects on airway secretion. Management of airway secretion is important, especially in patients with pneumonia. Generally, excessive secretion is a risk factor for NIV failure, and it was reported that NIV could not improve sputum clearance.[17] By contrast, HFNC was reported to improve airway clearance owing to the humidified air.[18] Therefore, HFNC might be more suitable for patients with excessive secretion.

There are some limitations to the present study. First, this was a retrospective study. Because there were no standardized protocols for HFNC, NIV, or IMV, their indications varied between patients. Second, the present study included patients with do-not-intubate orders. Although this represents real-world clinical practice, withholding treatments can affect patient outcomes. Third, although the cause of respiratory failure was classified according to a primary diagnosis made by each attending physician at discharge, some patients could have concurrent causes (e.g., pneumonia in patients with COPD). These concurrent causes could also influence the efficacy of respiratory support. Finally, we could not assess specific risk factors for treatment failure in

each subgroup. Although we included some common risk factors (e.g., respiratory rate, P/F ratio, and extrapulmonary SOFA score) in the multivariable analyses, some disease-specific risk factors might be more appropriate to adjust for the heterogeneity of patients.

CONCLUSION

IN THE PRESENT study, HFNC was associated with lower risk of 30-day mortality in patients with pneumonia or patients without hypercapnia, but a greater risk of treatment failure in patients with CPE or hypercapnia. High-flow nasal cannula oxygen therapy or NIV should be used in patients with etiologies appropriate to the type of respiratory support.

DISCLOSURE

Approval of the research protocol: The present study was approved by the institutional review board of each institution.
Informed consent: Because this was a retrospective review of medical records, consent to participate was not required from the patients.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None declared.

REFERENCES

1 Stefan MS, Shieh MS, Pekow PS *et al*. Epidemiology and outcomes of acute respiratory failure in the United States, 2001 to 2009: a national survey. J. Hosp. Med. 2013; 8: 76–82.
2 Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. Br. J. Anaesth. 2009; 103: 886–90.
3 Möller W, Feng S, Domanski U *et al*. Nasal high flow reduces dead space. J. Appl. Physiol. (1985) 2017; 122: 191–7.
4 Nagata K, Morimoto T, Fujimoto D *et al*. Efficacy of high-flow nasal cannula therapy in acute hypoxemic respiratory failure: decreased use of mechanical ventilation. Respir. Care 2015; 60: 1390–6.
5 Frat JP, Thille AW, Mercat A *et al*. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N. Engl. J. Med. 2015; 372: 2185–96.
6 Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst. Rev. 2013; CD005351.
7 Makdee O, Monsomboon A, Surabenjawong U *et al*. High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. Ann. Emerg. Med. 2017; 70: 465–72.
8 Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Non-invasive ventilation in acute cardiogenic pulmonary oedema. Postgrad. Med. J. 2005; 81: 637–43.
9 Kallet RH, Diaz JV. The physiologic effects of noninvasive ventilation. Respir. Care 2009; 54: 102–15.
10 Lee MK, Choi J, Park B *et al*. High flow nasal cannulae oxygen therapy in acute-moderate hypercapnic respiratory failure. Clin. Respir. J. 2018; 12: 2046–56.
11 Phua J, Kong K, Lee KH, Shen L, Lim TK. Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure. Intensive Care Med. 2005; 31: 533–9.
12 Jeong JH, Kim DH, Kim SC *et al*. Changes in arterial blood gases after use of high-flow nasal cannula therapy in the ED. Am. J. Emerg. Med. 2015; 33: 1344–9.
13 Carteaux G, Millán-Guilarte T, De Prost N *et al*. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. Crit. Care Med. 2016; 44: 282–90.
14 Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Crit. Care Med. 2012; 40: 1578–85.
15 Fraticelli AT, Lellouche F, L'her E, Taillé S, Mancebo J, Brochard L. Physiological effects of different interfaces during noninvasive ventilation for acute respiratory failure. Crit. Care Med. 2009; 37: 939–45.
16 Mauri T, Turrini C, Eronia N *et al*. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am. J. Respir. Crit. Care Med. 2017; 195: 1207–15.
17 Placidi G, Cornacchia M, Polese G, Zanolla L, Assael BM, Braggion C. Chest physiotherapy with positive airway pressure: a pilot study of short-term effects on sputum clearance in patients with cystic fibrosis and severe airway obstruction. Respir. Care 2006; 51: 1145–53.
18 Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. Chron. Respir. Dis. 2008; 5: 81–6.