Original Article

# Effect of high-flow nasal cannula oxygen therapy in combination with non-invasive ventilation on critically ill patients with acute respiratory failure: a retrospective study

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**Background:** Acute respiratory failure (ARF) is a respiratory disease in which ventilation dysfunction of the lungs occurs at rest due to various factors, resulting in oxygen deprivation and carbon dioxide ($CO_2$) retention. In recent years, high-flow nasal cannula (HFNC), as a new type of oxygen therapy, has attracted increasing attention. Compared with traditional oxygen therapy, HFNC adopts nasal catheter to make it more in line with the physiological and respiratory characteristics of the human body, and thus can provide a higher and more constant inhalation of oxygen. This retrospective study was conducted to explore the clinical effect of HFNC combined with non-invasive ventilation (NIV) in the treatment of critically ill patients with ARF.

**Methods:** A total of 532 critically ill patients with ARF treated in our hospital from January 2019 to December 2020 were screened for the suitability for being included in the study. Of these, 261 patients in this study received NIV. In total, 151 patients were included after applying the inclusion and exclusion criteria. NIV was generally given intermittently, and the daily duration of application was determined according to the patient's condition. The NIV-treated patients were assigned into two groups according to the oxygen inhalation mode during intermittent NIV: (I) standard group: normal oxygen inhalation was applied at the NIV interval; and (II) research group: patients treated with HFNC at the NIV interval. The respective basic data and outcome observation indices were collected.

**Results:** In terms of the clinical outcome, the number of NIV treatment days in the research group was lower ($P<0.05$). At 30 min, 1 h, and 24 h after treatment, the partial pressure of arterial oxygen ($PaO_2$), arterial oxygen saturation ($SaO_2$), oxygenation index (P/F) indices in the research group were higher, while the $CO_2$ partial pressure ($PaCO_2$) was lower ($P<0.05$). Finally, the 28- and 90-day survival rates were compared between the groups and the results indicated no significant difference in the 28-day survival rates, but the 90-day survival rates of the research group were considerably higher ($P<0.05$).

**Conclusions:** The use of HFNC combined with NIV to treat ARF in critically ill patients can effectively improve the ARF-related respiratory indicators in critically ill patients.

**Keywords:** High-flow nasal cannula (HFNC); non-invasive ventilation (NIV); acute respiratory failure (ARF)

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## Introduction

Acute respiratory failure (ARF) is a common hospitalization disease in intensive care units (ICUs) and has become a major issue which affects human health (1,2). According to statistics, millions of patients worldwide suffer from ARF every year, with a hospital mortality rate of 20.6% (3). Among these patients, approximately 42.1% require mechanical ventilation, greatly extending the length of hospital stay and expenses. Oxygen therapy is the first line treatment for acute hypoxic respiratory failure, in which conventional oxygen therapy is effective in improving the patient's ventilation status, but it is prone to be affected by the flow and type of breathing during treatment (4,5). Meanwhile, the patient's tolerance is poor and the prognosis is affected by insufficient gas heating and humidity. If the condition does not improve, escalation respiratory support therapy is required (5).

Non-invasive ventilation (NIV) is a common choice of treatment for patients with ARF in the emergency department, especially for patients with chronic obstructive pulmonary disease and acute pulmonary edema. However, NIV failure occurs in 10–40% of patients due to tight masks, discomfort with headbands, or gas leaks. NIV failure is an independent risk factor for poor prognosis in patients. For this reason, an approach that would be better tolerated is needed. High-flow nasal cannula (HFNC) oxygen is another oxygen therapy model that has evolved from nasal catheters. It can provide high flow of oxygen with stable oxygen concentration, achieving the goal of improving patient oxygen partial pressure (6). Numerous studies have confirmed that HFNC can flush the physiological dead space of the nasopharynx, generate lower levels of positive airway pressure to prevent alveolar collapse, stabilize oxygen concentration, reduce respiratory work, improve oxygenation, and improve patient comfort and tolerance (7-9). Alveolar collapse may lead to extensive affected area and thus increasing the severity [the formation of excessive dynamic airway collapse (EDAC)]. NIV and HFNC have shown positive effects in gas ventilation at lungs. They can improve oxygenation, reduce respiratory work, and achieve a more balanced ventilate flow ratio. Additionally, they can increase intrathoracic pressure, leading to decreased right cardiac venous return and reduced left ventricular transmural pressure. These unique advantages make NIV and HFNC widely utilized in various clinical settings (8,9).

The incidence and mortality rates of ARF are relatively high. Due to increased pulmonary capillary pressure, increased vascular permeability, extravasation of plasma, and fluid retention in the alveoli, patients with ARF experience pulmonary interstitial edema, gas exchange disorder, and an imbalance in blood flow and ventilation ratio, increasing the risk of hypoxia. If ARF is left untreated, the risk of death for patients is greatly increased. Therefore, active prevention and control of risk factors that may increase the failure rate of ventilation therapy in patients with ARF has become the focus of clinicians and patients. This study aims to evaluate the effectiveness and tolerability of HFNC combined with NIV in critically ill patients with ARF (7,9). We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1014/rc).

### Highlight box

**Key findings**

- The use of high-flow nasal cannula (HFNC) combined with non-invasive ventilation (NIV) can effectively improve the symptoms of acute respiratory failure (ARF)-induced dyspnea in critically ill patients.

**What is known and what is new?**

- ARF is a common disease which is characterized by the inability to perform efficient gas exchange. Respiratory failure occurs based on pulmonary ventilation and/or ventilation dysfunction induced by multiple factors.
- This retrospective study was conducted to explore the clinical effect of HFNC combined with NIV in the treatment of critically ill patients with ARF.

**What is the implication, and what should change now?**

- In this study, the clinical efficacies of patients treated with HFNC combined with NIV and nasal catheter or mask oxygen combined with NIV were observed. The effects of these two methods were compared.
- This study provides a scientific basis for the critical clinical treatment of ARF.

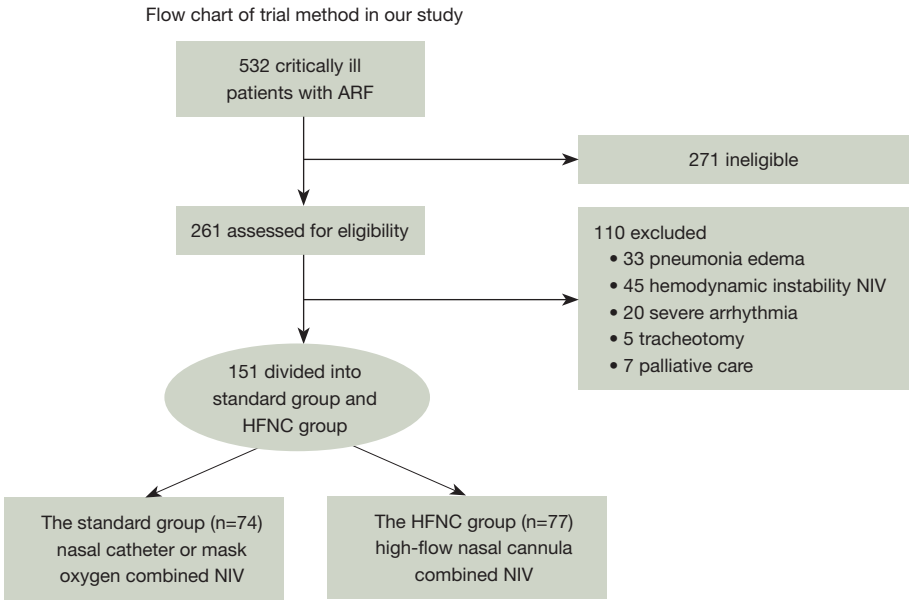


**Figure 1** Flow chart of trial method in this study. ARF, acute respiratory failure; NIV, non-invasive ventilation; HFNC, high-flow nasal cannula.

## Methods

### *Study protocol*

This is a retrospective observational study with the screening of 532 critically ill patients who were with ARF and treated in the intensive care unit (ICU) of our hospital (The Second Affiliated Hospital of Soochow University) from January 1, 2019 to December 31, 2020. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (No. JD-HG-2021-49). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients. Flow chart of the trial method in this study is shown in *Figure 1*.

#### Inclusion criteria

(I) Patients with ARF and NIV (ARF defined as: pulse oxygen saturation ($SpO_2$) <90%, arterial blood gas analysis with $PaO_2$ ≤60 mmHg, or $PO_2/FIO_2$ ≤300 mmHg); and (II) aged ≥18 years old.

#### Exclusion criteria

(I) Pulmonary edema; (II) hemodynamic instability [hemodynamic instability: mean arterial pressure (MAP) <65 mmHg, or the use of vasoactive drugs such as norepinephrine or dopamine]; (III) severe arrhythmias: arrhythmias affecting hemodynamic stability and/or life-threatening arrhythmias, such as rapid supraventricular arrhythmias (rapid atrial tachycardia, atrial fibrillation), new frequent ventricular premature beats, short ventricular tachycardia, etc.; (IV) post-tracheotomy; and (V) palliative treatment.

### *Treatment methods*

The NIV-treated patients were assigned into two groups according to the oxygen inhalation mode during intermittent NIV: (I) standard group: normal oxygen inhalation applied at the NIV interval; and (II) research group: patients treated with HFNC at the NIV interval. Patients in both groups were given basic treatment in areas such as anti-infection, phlegm reduction, and maintaining a stable internal environment. Moreover, the standard group was treated with MAQUET SERVO-s ventilator, by maintaining tidal volume of 7–10 mL/kg, positive end-expiratory pressure (PEEP) of 2–10 $cmH_2O$, and titrating $FiO_2$ to maintain $SpO_2$ ≥92%.

The high flow oxygen group was treated with a high flow oxygen inhalation device (AIRVO2, Fisher Paykel, New Zealand) with an inhalation flow rate of 20–60 L/min and an inhalation oxygen concentration of 21–100% in order to maintain carbon dioxide ($CO_2$) >50 mmHg and

 

$SpO_2$ ≥92%. If the condition of the patients became severe, tracheal intubation and ventilator assisted ventilation were arranged, given that, the patients experienced the following conditions: (I) hemodynamic instability; (II) worsening of neurological condition; (III) worsening of respiratory failure, respiratory rate >40/min, the need to assist respiratory muscles to participate in respiration; (IV) PH (hydrogen ion concentration) <7.35, $SpO_2$ <90%, lasting for more than 5 min.

### *Recorded data*

#### General information

A total of 261 cases in this study received NIV. Finally, 151 patients were included after applying the inclusion and exclusion criteria. NIV was generally given intermittently, and the daily duration of application was determined according to the patient's condition. The NIV-treated patients were assigned into two groups according to the oxygen inhalation mode during intermittent NIV: the standard group and the HFNC group. The standard group (n=74) received nasal catheter or mask oxygen combined with NIV, and the HFNC group (n=77) received high-flow oxygen through a nasal cannula combined with NIV. Clinical data such as age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE)-II, cause of respiratory failure, lung disease, vital signs, oxygenation index, and lactic acid level were recorded.

#### Clinical outcomes

The number of NIV treatment days, the length of ICU hospitalization, the total length of hospitalization, the duration of invasive ventilation, and the cost of hospitalization were calculated.

#### Blood gas analysis results

The results of partial pressure of arterial oxygen ($PaO_2$), arterial oxygen saturation ($SaO_2$), arterial blood $CO_2$ partial pressure ($PaCO_2$), and oxygenation index (P/F) were calculated before and at 0.5, 1, and 24 h following treatment initiation.

#### Curative effect

(I) Improvement: after treatment, symptoms including cough, expectoration, wheezing, and dyspnea were remarkably improved; the indices of blood gas analysis were markedly improved or getting normal; and the oxygen therapy method was finally changed to ordinary oxygen inhalation (nasal cannula oxygen inhalation). The rate-oxygenation index (ROX) assesses respiratory distress by measuring the ratio of oxygen saturation to the fraction of inspired oxygen ($SpO_2/FiO_2$) in patients. In the study, ROX was calculated using $SpO_2$ and $FiO_2$ values obtained through pulse oximetry and ventilator settings, respectively. The visual analogue scale (VAS) is a subjective pain assessment tool with which patients rate pain intensity on a 10 cm line. In the study, participants marked the line to indicate their pain level, with higher scores indicating more severe pain.

(II) Ineffective: cough, expectoration, wheezing, dyspnea, and blood gas analysis indices showed no remarkable change or aggravation tendency before and after treatment, or ineffective treatment leading to tracheal intubation, mechanical ventilation, or death.

#### Survival rates at 28 and 90 days

Analyses were performed on the 28- and 90-day survival rates using Kaplan-Meier curves.

### *Statistical analysis*

SPSS 26.0 (SPSS, Chicago, USA) was employed for statistical analysis. As a result of the normality test, the measurement data were displayed as mean ± standard deviation if they followed the normal distribution, and the paired *t*-test was employed. However, measurement data of non-normal distribution were presented by the median and quartile interval [M (Q25–Q75)], and Wilcoxon signed-rank test was employed. Survival time was analyzed by Cox regression (P<0.05).

## Results

### *Comparison of clinical data of patients*

There was no difference in age, sex, BMI, APACHE-II, causes of respiratory failure, bilateral lung disease, respiratory rate, heart rate, blood pressure, arterial blood gas, oxygenation index, and lactic acid level (P>0.05, *Table 1*).

### *Comparison of clinical outcomes*

Clinical outcomes were compared between the standard group and the HFNC group, and the results showed that the number of days of NIV treatment was lower in the

**Table 1** Clinical data between two groups of patients

| Variables | Standard group (n=74) | HFNC group (n=77) | $t/\chi^2/U$ | P |
|---|---|---|---|---|
| Age (years) | 67.78±16.82 | 66.97±17.08 | 0.293 | 0.77 |
| Male | 55 (74.3) | 46 (59.7) | 3.624 | 0.075 |
| BMI (kg/m$^2$) | 23.10±4.15 | 23.46±4.13 | –0.527 | 0.599 |
| APACHE-II | 17.51±5.47 | 17.78±5.44 | –0.299 | 0.756 |
| Causes of respiratory failure | | | 4.272 | 0.37 |
| CAP | 35 (47.3) | 29 (37.7) | 1.85 | 0.4 |
| HAP | 9 (12.2) | 11 (14.3) | 0.366 | 0.61 |
| AECOPD | 15 (20.3) | 11 (14.3) | 1.254 | 0.64 |
| Extrapulmonary sepsis | 7 (9.5) | 12 (15.6) | 1.256 | 0.65 |
| Other | 8 (10.8) | 14 (18.2) | 0.958 | 0.58 |
| Bilateral lung disease | 71 (95.9) | 73 (94.8) | 0.111 | 0.739 |
| Respiratory rate (times/min) | 26.22±7.28 | 24.83±5.98 | 1.277 | 0.204 |
| Heart rate (beats/min) | 103.81±20.43 | 107.39±25.22 | –0.955 | 0.341 |
| Blood pressure (mmHg) | | | | |
| SAP | 134.52±24.70 | 132.07±27.91 | 0.566 | 0.572 |
| MAP | 96.07±17.82 | 91.36±17.52 | 1.632 | 0.105 |
| Arterial blood gases | | | | |
| pH | 7.37±0.12 | 7.40±0.10 | –1.529 | 0.128 |
| $PaCO_2$ (mmHg) | 47.57±25.4 | 42.40±18.06 | –0.866 | 0.387 |
| $PaO_2$ (mmHg) | 102.55±53.07 | 97.96±49.25 | 0.552 | 0.582 |
| Oxygenation index | 226.50±103.93 | 225.20±99.67 | 0.078 | 0.938 |

Data are presented as n (%) or mean ± standard deviation. BMI, body mass index; APACHE-II, Acute Physiology and Chronic Health Evaluation-II; CAP, community-acquired pneumonia; HAP, hospital acquired pneumonia; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; SAP, stroke-associated pneumonia; MAP, mean arterial pressure; $PaCO_2$, carbon dioxide partial pressure; $PaO_2$, partial pressure of arterial oxygen.

HFNC group (P<0.05). There were no marked differences in the length of ICU hospitalization, total length of stay, invasive ventilation time, or ICU hospitalization cost (P>0.05), but there was a significant difference in ROX, and VAS scores between the two groups of patients (P<0.05, *Table 2*). NIV and HFNC are two forms of respiratory support for patients with respiratory failure prior to invasive ventilation. In recent years, the use of HFNC has been increasing, and delayed intubation caused by HFNC use would increase the mortality of patients. Therefore, the ROX index is proposed to guide for the timing to administer endotracheal intubation in HFNC. Interestingly, there was no significant difference in the length of invasive ventilation time, but there was a significant difference in the ROX index. In addition, the VAS scores were apparently decreased in the HFNC group compared to the standard group.

### *$PaO_2$, $PaCO_2$, P/F, and $SaO_2$ indices comparison*

Then, the indices of $PaO_2$, $PaCO_2$, P/F, and $SaO_2$ were compared between the standard group and the HFNC group. Before treatment, no marked differences were observed in $PaO_2$, $PaCO_2$, P/F, and $SaO_2$ (P>0.05). At 30 min, 1 h, and 24 h after treatment, the indices of $PaO_2$, P/F, and $SaO_2$ in the research group were higher, while $PaCO_2$ was lower (P<0.05, *Figure 2*).

**Table 2** Subjects' outcomes between the two groups ($\bar{x}$±s)

| Group | Standard group (n=74) | HFNC group (n=77) | $t/\chi^2/U$ | P |
|---|---|---|---|---|
| NIV treatment duration (days) | 5.93±4.02 | 4.22±2.12 | –3.253 | 0.002 |
| Length of stay in the ICU (days) | 9.89±6.87 | 10.34±11.27 | –0.292 | 0.771 |
| Total length of hospital stay (days) | 18.41±14.42 | 20.27±18.73 | –0.679 | 0.498 |
| Invasive ventilation duration (days) | 2.70±5.97 | 2.35±10.74 | 0.247 | 0.805 |
| Hospitalization expenses (yuan) | 92,867.76±83,518.55 | 91,848.42±95,841.43 | 0.066 | 0.947 |
| ROX index | 3.79±0.41 | 4.63±0.59 | 10.190 | <0.001 |
| VAS | 3.24±0.48 | 5.67±0.83 | 21.910 | <0.001 |

HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; ICU, intensive care unit; ROX, rate-oxygenation index; VAS, visual analogue scale.

### *Comparison of curative effect*

The results demonstrated that 51 cases were improved, 26 cases were ineffective, and the effective rate was 66.20% in the HFNC group. Meanwhile, 44 cases were improved, 30 cases were ineffective in the standard group, and the effective rate was 59.50%. No notable difference was observed in the curative effect (P>0.05, *Figure 3*).

### *Survival rates at 28 and 90 days*

Survival rates were compared between the standard and HFNC groups at 28 and 90 days. Results showed no significant difference in 28-day survival, but the 90-day survival rate was significantly higher in the HFNC group (P<0.05, *Figure 4*).

## Discussion

ARF, as a common clinical medical disease, is mainly caused by airway obstruction, pleural disease or other basic diseases. In the past, ARF was treated with antimicrobials, anti-spasmodic and bronchodilation, which can improve dyspnea and hence relieve from shortness of breath and related features (10,11). It is particularly important to choose scientific and reasonable treatment methods. As a less used treatment method, NIV assisted mode has remarkable characteristics such as being non-invasive and effective, which can alleviate clinical symptoms such as dyspnea and cyanosis to a great extent, and ensure that patients can obtain sufficient oxygen through airway remodeling, so as to meet the oxygen consumption need of the body (12-15).

Currently, the clinical treatment of ARF is based on making the airways unobtrusive in the shortest period of time and giving the patient oxygen inhalation with increased ventilation to relieve severe hypoxia and reduce $CO_2$ retention (15). Ventilation therapy is an important therapy in the clinical treatment of patients with ARF. HFNC can provide the oxygen concentration and oxygen flow required by the body, ensure the oxygen relative humidity, reduce the resistance of the upper respiratory tract, and reduce the energy consumption of the body, effectively relieve the hypoxia state of patients with ARF and reduce the degree of $CO_2$ retention in the body, so as to promote relief from clinical symptoms (15-18). However, there are still some patients whose condition cannot be effectively controlled after the ventilation treatment, and some patients even experience aggravation, increasing the risk of death (19-22). The results of the current study showed that the number of days of NIV treatment was lower in the HFNC group. Moreover, the invasive ventilation time was reduced in the HFNC group compared to the standard group based on the ROX index. In the HFNC group, ROX index was significantly higher. Interestingly, there was no significant difference in the length of invasive ventilation time, but there was a significant difference in the ROX index. In addition, the VAS scores were apparently decreased in the HFNC group.

No statistical difference was found in the curative effect between the control and research groups, which may be related to the general condition of the two groups of patients. However, by comparing the relevant results of the arterial blood gas analysis, we found that the relevant respiratory parameters ($PaO_2$, P/F, $SaO_2$) of the patients in the study group at 30 min, 1 h, and 24 h after treatment

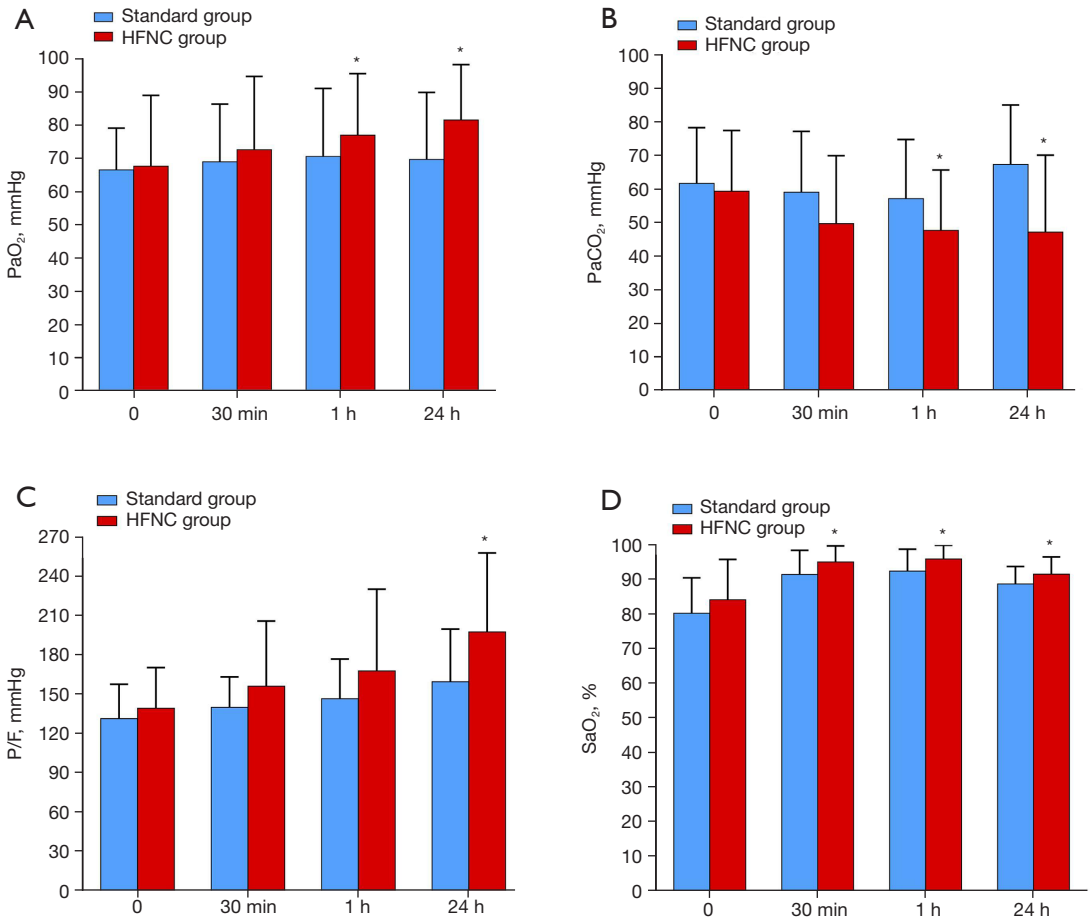


**Figure 2** Comparison of (A) $PaO_2$, (B) $PaCO_2$, (C) P/F, (D) $SaO_2$ indexes between two groups. *, *vs.* standard group, P<0.05. $PaO_2$, partial pressure of arterial oxygen; $SaO_2$, arterial oxygen saturation; P/F, oxygenation index; $PaCO_2$, carbon dioxide partial pressure; HFNC, high-flow nasal cannula.

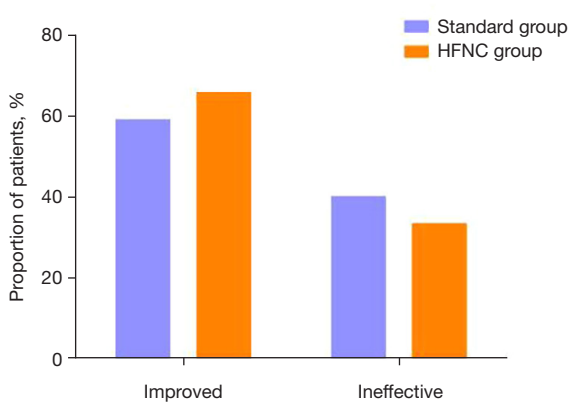


**Figure 3** Comparison of curative effect. HFNC, high-flow nasal cannula.

were higher than those in the observation group, while the $PaCO_2$ indexes were lower (P<0.05). The reasons for this may be as follows: high-flow oxygen inhalation through the nose can not only ensure a higher oxygen concentration but also plays an important role in humidifying the airway; flushing the nasopharynx with a higher oxygen flow may be beneficial to expel $CO_2$ (23). With the use of HFNC in patients with acute respiratory failure, researchers observed a significant improvement in oxygenation, as indicated by higher ROX index values, compared to standard oxygen therapy. This finding echoes the results of our study, reinforcing the notion that HFNC can be a beneficial intervention for patients requiring respiratory support (24,25). Grieco *et al.* did a randomized controlled trial

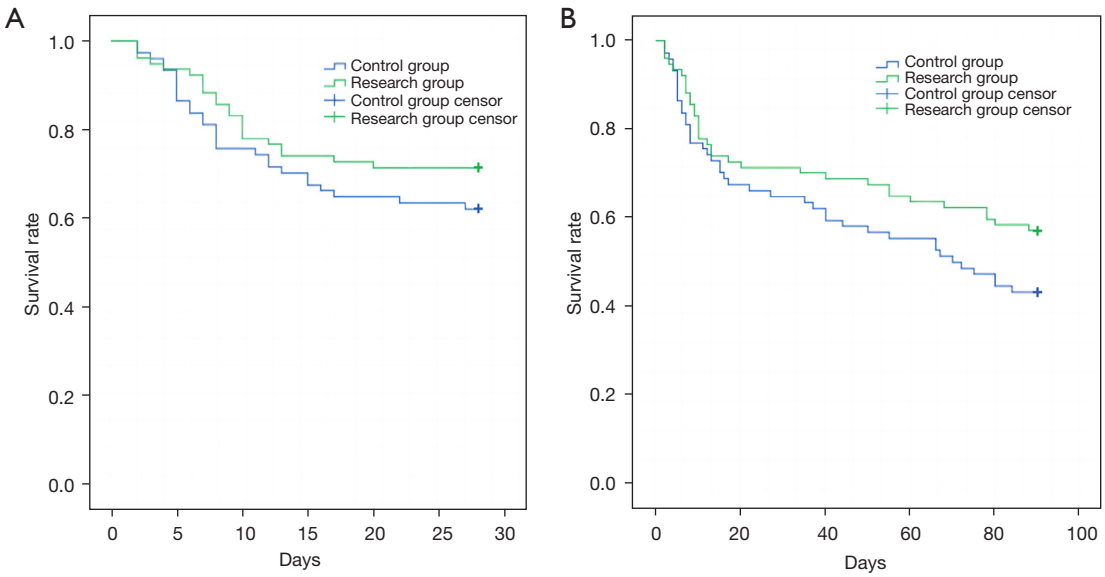


**Figure 4** The Kaplan-Meier curves display the survival rate at 28 days (A) and 90 days (B).

comparing HFNC to NIV in patients with acute hypoxemic respiratory failure and reported comparable improvements in oxygenation and respiratory rates between the HFNC and NIV groups, with no significant differences in ROX index values (23-25). Other studies support the notion that HFNC can be as effective as other NIV methods in certain clinical contexts. Several studies explored the use of HFNC in patients with acute hypoxemic respiratory failure in the ICU (25-27). Although the ROX index was not explicitly used in this study, the findings align with the broader consensus on the positive impact of HFNC on respiratory outcomes (26,27). In a study of 42 elderly patients with chronic obstructive pulmonary disease and asthma, Li *et al.* (23) showed that inhaling high-flow humidified oxygen therapy improved patients' arterial $PaCO_2$, $SaO_2$, and other clinical indicators better than conventional oxygen therapy. To some extent, that study also supports the ideas of our paper. In addition, nasal high-flow oxygen can also generate a certain amount of PEEP, which may be an important reason for shortening the number of NIV treatment days (24-29).

High-flow oxygen yields less frequent use of rescue NIV. Related studies have also reported similar results (30,31). In critically ill patients with ARF, the diaphragm and external intercostal muscles strengthen the contraction during forced inspiration due to dyspnea, and the auxiliary inspiratory muscles also participate in work. The longer the duration, the more serious the pulmonary gas exchange dysfunction (32-34).

The results of the current study showed that 90-day survival was significantly higher in the HFNC group than in the standard group, but there was no significant difference in 28-day survival, which is consistent with the Cammarota *et al.*'s study report (1). It is difficult to properly explain the differences in the 28- and 90-day survival rates, which also reflects the limitations of this study. Firstly, this is a retrospective study conducted at a single center, and thus, the sample size was small. Our future research plans to include multi-center, large-scale prospective studies of samples, from which more valuable conclusions could be drawn.

In conclusion, nasal high-flow humidification therapy can be more widely used in clinical practice. Its combination with non-invasive positive pressure ventilation for the treatment of critically ill patients with ARF can successfully enhance the relevant respiratory indicators of patients, reduce the number of NIV treatment days, and increase the 90-day survival rate. This study may have potential biases. These include selection bias, potentially skewing patient representation. Information bias may arise from data accuracy in medical records. Confounding variables, not controlled for, could influence intervention effectiveness. Lead-time and survivorship biases might affect the observed outcomes. Acknowledging and addressing these biases are crucial for accurate interpretation of the study's findings. HFNC can provide stable oxygen concentrations at high flow rates while also producing a certain positive airway

pressure, which plays a positive role in improving the hypoxia status of the patients.

## Conclusions

The use of HFNC combined with NIV to treat ARF in critically ill patients can effectively improve the ARF-related respiratory indicators in critically ill patients.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1014/rc

*Data Sharing Statement:* Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1014/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1014/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (No. JD-HG-2021-49). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients.



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