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Original Article

Clinical effect of high-flow nasal cannula oxygen therapy combined with naloxone on severe respiratory failure in older adult patients: a randomized controlled trial

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Abstract: Objective: To analyze the clinical effect of high-flow nasal cannula (HFNC) oxygen therapy combined with naloxone on severe respiratory failure (SRF) in older adult patients. Methods: We enrolled 96 older adult patients with SRF who were admitted to Hai'an People's Hospital between February 2019 and March 2022. The patients were divided into two groups: the control group (treated with non-invasive positive pressure ventilation combined with naloxone) and the observation group (treated with HFNC oxygen therapy combined with naloxone). The blood gas measurement, respiratory rate (RR), St. George's Respiratory Questionnaire (SGRQ) score, Clara cell secreted protein (CC16) level, tumor necrosis factor-alpha (TNF-α) level, interleukin-1 (IL-1) level, length of intensive care unit (ICU) stay, tracheal intubation rate, and 28-day mortality rate were compared between the groups. Results: Blood gas measurement or RR did not differ significantly between the groups (P>0.05). The observation group showed improved outcome, including reduced partial pressure of CO_2, RR, and pH, and increased partial pressure of O_2 (PaO_2), PaO_2/fraction of inspired O_2 ratio, and O_2 saturation after treatment (P<0.05). Additionally, the observation group exhibited lower TNF-α level, IL-1 level, and SGRQ score, and higher CC16 level (P<0.05). The length of ICU stay, tracheal intubation rate, and 28-day mortality rate were lower in the observation group (P<0.05). Conclusions: HFNC oxygen therapy combined with naloxone in older adult patients with SRF could improve blood gas results, disease duration, tracheal intubation rate, and 28-day mortality rate. This may occur through regulation of TNF-α, IL-1, and CC16 expression.

Keywords: Blood gas indicators, high-flow nasal cannula, naloxone, older adults, severe respiratory failure

Introduction

Respiratory failure is a common and severe disease in the older adult population. Severe respiratory failure (SRF) is a common clinical emergency and a key clinical manifestation of cardiac and respiratory disorders [1]. To date, the number of emergency department visits of older adults has increased [2]. Moreover, they have reduced lung capacity, high metabolism because of weakened bodily functions and comorbidities, and a negative nitrogen balance, which aggravate respiratory muscle weakness and respiratory dysfunction, leading to respiratory failure.

Causal factors of SRF include ventilation/perfusion mismatch, dispersion dysfunction, and decreased arterial partial pressure of oxygen (PaO_2) [3]. In older adult patients, physiological decline comorbid with underlying diseases may lead to poor tolerance to hypoxia and poor SRF prognosis [4]. Currently, the clinical treatment of SRF includes medication and non-invasive positive pressure ventilation. For example, naloxone, a commonly used drug for SRF, can reverse central nervous system (CNS) depression and improve respiratory function [5].

Non-invasive positive pressure ventilation can improve hypoxia but causes nasal dryness, gastric distention, and pneumothorax, which lowers the patients' quality of life (QOL) [6]. High-flow nasal cannula (HFNC) oxygen therapy can overcome the disadvantages of non-invasive positive pressure ventilation by creating posi-

tive end-expiratory pressure in the airway, promoting alveolar reopening, increasing end-expiratory volume, heating and humidifying inhaled gas, relieving small airway spasms caused by cold stimulation, and promoting respiratory secretion clearance by improving ciliary motor function [7]. The use of non-invasive-assisted ventilation or medication alone has been extensively studied, but medication-assisted non-invasive ventilation is poorly explored. Therefore, this study aimed to investigate the efficiency of high-flow nasal cannula oxygen therapy combined with naloxone to treat SRF in older adult patients. The treatment effects included improved blood gas measurements, shortened disease course, and reduced tracheal intubation and 28-day mortality rates. This may have been related to regulation of the expression of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and Clara cell secreted protein (CC16).

Materials and methods

Patient selection

In this randomized controlled trial, we enrolled older adult patients with SRF admitted to Hai'an People's Hospital from February 2019 to March 2022. The sample size was determined using the sample size estimation formula for comparing the mean of two samples [8]: $n_1=n_2=2*\left[\frac{(t_\alpha + t_\beta) * s}{\delta}\right]^2$, with a 0.05 margin of error, and 95% confidence level, α=0.05, β=0.1, we can obtained from the t-value table: t_α=1.96, t_β=1.28, and our s=0.28, δ=0.19, therefore $n=2*\left[\frac{(1.96 + 1.28) * 0.28}{0.19}\right]^2=46$. The inclusion criteria were as follows: (1) a diagnosis of respiratory failure based on a PaO_2/fraction of inspired oxygen (FiO_2) <300 mmHg, arterial blood gas pH >7.25, arterial partial pressure of carbon dioxide ($PaCO_2$) >50 mmHg, and PaO_2 <60 mmHg [9]; and (2) age ≥60 years. The exclusion criteria were as follows: (1) contraindications for naloxone administration, such as allergy; (2) solid malignancies or hematopoietic or immune system diseases; (3) indications for emergency tracheal intubation; (4) previous chronic liver or kidney diseases; (5) facial trauma or deformity; (6) hemodynamic instability requiring vasoactive medications; (7) massive hemoptysis or epistaxis; and (8) mental disorders.

The patients were divided into observation and control groups through single-blinded simple randomization using a random number table and a sealed envelope system. Matching was performed for the two groups in terms of general characteristics in accordance with the CONSORT guidelines [10]. The study protocol was approved by the Medical Ethics Committee of the Hai'an People's Hospital on December 21, 2018 (approval number: HKL-201841). Informed consent was obtained from patients or their guardians. The study was registered with the China Clinical Trial Center (registration number: ChiCTR2300075392).

Method

Patients in both groups were actively treated for the primary disease with symptomatic relief using anti-inflammatory drugs, expectorants, anti-asthmatic drugs, and fluid infusion. The patients in the control group were treated with non-invasive positive pressure ventilation using a Philips Respironics V60 ventilator combined with naloxone (GUOYAOZHUNZI H20055761, Sihuan Pharmaceutical Co., Ltd., Beijing, China). The positive end-expiratory pressure was set to >2 cmH_2O, and the tidal volume was set to 6-10 mL/kg. The inhaled oxygen concentration was set to maintain blood oxygen saturation (SaO_2) <92%. Naloxone (0.4-0.8 mg) was added to a 250-mL intravenous drip of 5% glucose daily for 7 days. The observation group was treated using HFNC oxygen therapy combined with naloxone. HFNC was manufactured by Fisher & Paykel Healthcare (Aucklang, New Zealand). The HFNC parameters were as follows: temperature, 37°C; gas flow rate, 50 L/min; initial oxygen concentration, 100%; and adjusted oxygen concentration to maintain SaO_2, 92%. The naloxone dosage was the same as that of the control group. When patients' condition changed during the study period, requiring other treatment methods (e.g., invasive ventilation), they received the appropriate treatment.

Observation indicators and detection methods

The primary outcome measure was pH. The secondary outcome measures were the PaO_2, $PaCO_2$, RR, CC16, TNF-α, IL-1, and SaO_2 levels as well as the PaO_2/FiO_2 ratio, St. George's Respiratory Questionnaire (SGRQ) score, ICU

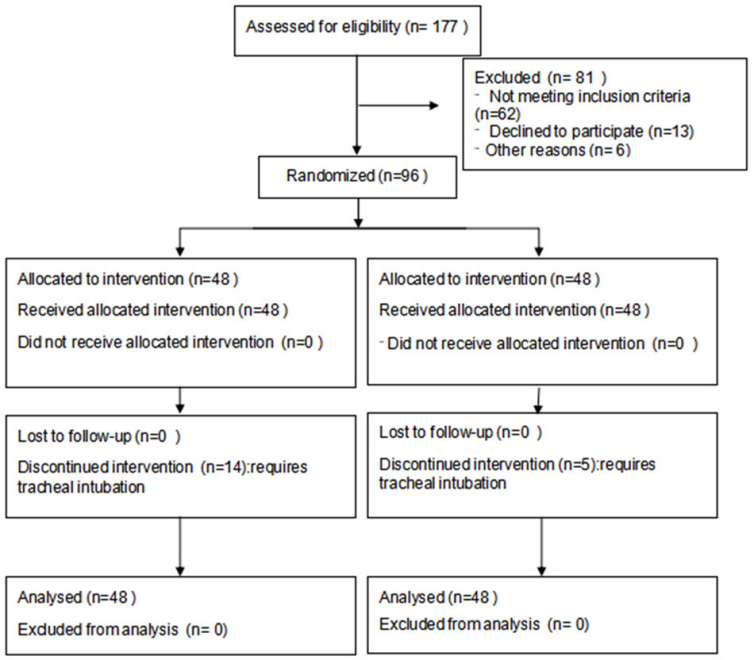

Figure 1. Flowchart of the study.

duration, tracheal intubation rate, and 28-day mortality rate. Before and at 7 days after treatment, 3 mL of peripheral venous blood was drawn from the patients who had fasted for >8 h before blood collection. Blood samples were collected and centrifuged within 1 h at 3,000 rpm for 10 min. The CC16 (ml025369), TNF-α (ml077385), and IL-1 (ml058034) levels were detected using an enzyme-linked immunosorbent assay kit (Mindray RT-96; Shanghai Enzyme-linked Biological Technology Co., Ltd., Shanghai, China).

The ICU duration, acute physiology and chronic health evaluation scoring system II (APACHE II), tracheal intubation rate, and 28-day mortality rate were recorded in both groups. The patients' QOL was quantified using the SGRQ score on the 3rd day after treatment [11]. The SGRQ includes three parts: respiratory symptoms, impact on daily life, and activity, with a total of 50 items. The score is assigned on a percentage scale, where a higher score indicates a low QOL, and vice versa.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Blood gas measurements and the CC16, TNF-α, and IL-1 levels conforming to normal distribution were expressed as means ± standard errors of the mean. Paired samples t-tests were used for within-group comparisons, and independent samples t-tests were used for between-group comparisons. Multi-time data were analyzed using repeated measures ANOVA along with post-hoc Bonferroni correction. Counted data were expressed as numbers (%) of cases; the χ^2 test was used for comparison. A p-value <0.05 was set to indicate significance.

Results

Participant flow

In total, 96 patients were enrolled. The control group constituted 48 patients, including 26 (54.17%) men and 22 (45.83%) women (mean age, 69.12±5.58 [range: 60-85] years). The observation group constituted 48 patients, including 24 (50.00%) men and 24 (50.00%) women (mean age, 69.82±5.94 [range: 60-86] years). **Figure 1** shows the flowchart of this process.

Comparison of general characteristics between the two groups

Sex, age, PaO_2/FiO_2, APACHE II score, causes of dyspnea, comorbidities, smoking history, or other baseline data did not differ significantly between the two groups (P>0.05; **Table 1**).

Comparison of blood gas measurements and respiratory frequency between the two groups

Before treatment, blood gas measurements or respiratory rates (RRs) did not differ significantly between the two groups (P>0.05). After 2 and 3 days of treatment, $PaCO_2$, RR, and pH decreased in both groups. After 2 days of treatment, PaO_2, PaO_2/FiO_2, and SaO_2 were higher, and blood gas measurements and RR were significantly better in the observation than in the control group (P<0.05; **Table 2**). After repeated measures ANOVA and Bonferroni post-hoc multiple tests, the RR main effect of intervention

Table 1. Comparison of general data between the two groups (n=96)

Information	Control group (n=48)	Observation group (n=48)	χ^2 or t	*p*-value
Sex, n (%)			0.167	0.683
Male	26 (54.17)	24 (50.00)		
Female	22 (45.83)	24 (50.00)		
Age	69.12±5.58	69.82±5.94	0.595	0.553
PaO_2/FiO_2, mmHg	162.02±24.53	158.98±28.11	0.565	0.574
APACHE II score, points	18.52±3.23	17.98±2.24	0.952	0.345
Causes of breathing difficulties (%)			1.162	0.762
Lung infection	17 (35.42)	13 (27.08)		
Severe pneumonia	21 (43.75)	24 (50.00)		
Pulmonary Edema	6 (12.50)	8 (16.67)		
Other	4 (8.33)	3 (6.25)		
Smoking history n (%)			0.222	0.637
Yes	11 (22.92)	13 (27.08)		
No	37 (77.08)	35 (72.92)		
Concomitant disease n (%)				
Hypertension	11 (22.92)	9 (18.75)	0.253	0.615
Diabetes	8 (16.67)	6 (12.50)	0.335	0.563
Coronary heart disease	10 (20.83)	13 (27.08)	0.515	0.473

The values are presented as means ± standard error of the mean. FiO_2, fraction of inspired oxygen; PaO_2, Arterial partial pressure of oxygen.

Table 2. Comparison of blood gas indexes and respiratory rate between the two groups (n=96)

Index	Time	Control group n=48	Observation group n=48	*t*	*p*-value
RR (times/min)	Before therapy	35.25±4.02	34.98±3.85	0.336	0.738
	Treatment 2 d	27.25±3.45*	23.82±3.26*	5.006	0.000
	Treatment 3 d	23.21±2.58*	21.23±2.19*	4.054	0.000
pH	Before therapy	7.63±0.23	7.59±0.21	0.890	0.376
	Treatment 2 d	7.34±0.20*	7.15±0.16*	4.013	0.000
	Treatment 3 d	7.21±0.21*	7.09±0.23*	2.669	0.009
PaO_2 (mmHg)	Before therapy	49.11±4.38	50.28±4.13	1.346	0.181
	Treatment 2 d	66.41±4.31*	72.25±4.25*	6.684	0.000
	Treatment 3 d	78.25±3.96*	84.11±3.26*	7.915	0.000
$PaCO_2$ (mmHg)	Before therapy	68.15±4.13	67.98±4.27	0.198	0.843
	Treatment 2 d	59.63±4.44*	53.14±4.03*	7.499	0.000
	Treatment 3 d	48.23±3.89*	42.53±3.74*	7.318	0.000
PaO_2/FiO_2 (mmHg)	Before therapy	162.02±24.53	158.98±28.11	0.565	0.574
	Treatment 2 d	201.63±21.59*	224.89±23.04*	5.104	0.000
	Treatment 3 d	231.05±25.85*	254.56±22.87*	4.719	0.000
SaO_2 (%)	Before therapy	76.96±5.44	74.86±5.65	1.855	0.067
	Treatment 2 d	88.14±4.78*	93.36±3.12*	6.336	0.000
	Treatment 3 d	93.12±3.01*	96.44±2.25*	6.121	0.000

*Compared to the same group before treatment, $P<0.05$. The values are presented as means ± standard error of the mean. d, days; FiO_2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, Arterial partial pressure of oxygen; RR, respiratory rates; SaO_2, blood oxygen saturation.

between the groups and time was significant, and there was an interaction between groups and time ($P<0.05$). Moreover, the differences between the two groups were significant when

Table 3. Comparison of blood gas indexes and respiratory rates between the two groups (n=96)

Index	Time	Control group n=48	Observation group n=48	Interblock		Time		Interaction	
				F	*p*-value	F	*p*-value	F	*p*-value
RR (times/min)	Before therapy	35.25±4.02	34.98±3.85	155.729	<0.001	254.167	<0.001	40.990	<0.001
	Treatment 2 d	27.25±3.45*	23.82±3.26*,#						
	Treatment 3 d	23.21±2.58*	21.23±2.19*,#						
pH	Before therapy	7.63±0.23	7.59±0.21	48.596	<0.001	87.543	<0.001	13.614	<0.001
	Treatment 2 d	7.34±0.20*	7.15±0.16*,#						
	Treatment 3 d	7.21±0.21*	7.09±0.23*,#						
PaO_2 (mmHg)	Before therapy	49.11±4.38	50.28±4.13	291.078	<0.001	927.436	<0.001	121.851	<0.001
	Treatment 2 d	66.41±4.31*	72.25±4.25*,#						
	Treatment 3 d	78.25±3.96*	84.11±3.26*,#						
$PaCO_2$ (mmHg)	Before therapy	68.15±4.13	67.98±4.27	277.145	<0.001	485.582	<0.001	76.273	<0.001
	Treatment 2 d	59.63±4.44*	53.14±4.03*,#						
	Treatment 3 d	48.23±3.89*	42.53±3.74*,#						
PaO_2/FiO_2 (mmHg)	Before therapy	162.02±24.53	158.98±28.11	99.530	<0.001	186.893	<0.001	28.642	<0.001
	Treatment 2 d	201.63±21.59*	224.89±23.04*,#						
	Treatment 3 d	231.05±25.85*	254.56±22.87*,#						
SaO_2 (%)	Before therapy	76.96±5.44	74.86±5.65	160.361	<0.001	419.920	<0.001	58.028	<0.001
	Treatment 2 d	88.14±4.78*	93.36±3.12*,#						
	Treatment 3 d	93.12±3.01*	96.44±2.25*,#						

*Compared to the same group before treatment, *P*<0.05. #Compared to the control group at the same time, *P*<0.05. The values are presented as means ± standard errors of the mean. d, days; FiO_2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, Arterial partial pressure of oxygen; RR, respiratory rates; SaO_2, blood oxygen saturation.

Table 4. Comparison of the CC16, TNF-α, and IL-1 levels between the two groups (n=96)

Group	n	CC16 (ng/mL)		TNF-α (ng/mL)		IL-1 (pg/mL)	
		Before	After	Before	After	Before	After
Control group	48	4.52±1.05	6.28±1.23*	12.58±2.01	7.24±1.56*	21.25±3.39	11.41±2.13*
Observation group	48	4.46±1.17	7.45±1.41*	12.63±1.89	5.03±0.89*	20.97±3.47	5.82±1.92*
t		0.264	4.332	0.126	8.525	0.400	13.505
p-value		0.792	0.000	0.900	0.000	0.690	0.000

*Represents the comparison to the control group, *P*<0.05. CC16, Clara cell secreted protein; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

comparing the findings of the two groups at 2 and 3 days after treatment with the corresponding obtained in the pre-treatment period (*P*<0.05). Finally, the differences between the observation group at 2 days and 3 days after treatment and the control group were significant (*P*<0.05; **Table 3**).

Comparison of the CC16, TNF-α, and IL-1 levels between the two groups

Before treatment, the CC16, TNF-α, or IL-1 levels did not differ significantly between the two groups (*P*>0.05). In both groups after treatment, the TNF-α levels, IL-1 levels, and SGRQ scores decreased, while the CC16 levels increased. The decrease in the TNF-α levels, IL-1 levels, and SGRQ scores and the increase in the CC16 levels after treatment were significantly better in the observation than in the control group (*P*<0.05; **Table 4**).

Comparison of the SGRQ scores between the two groups

Before treatment, the SGRQ scores did not differ significantly between the two groups (*P*>0.05). In both groups after treatment, the SGRQ scores decreased. This decrease was significantly better in the observation group than in the control group (*P*<0.05; **Table 5**).

Comparison of rehabilitation-related indices between the two groups

The length of ICU stay was significantly shorter in the observation group than in the control

Table 5. Comparison of the SGRQ scores (points) between the two groups (n=96)

Group	n	SGRQ score	
		Before	After
Control group	48	68.89±4.96	54.28±4.17*
Observation group	48	69.13±5.22	49.53±3.98*
t		0.231	5.709
p-value		0.818	0.000

*Represents the comparison with the control group, $P<0.05$. SGRQ, St. George's Respiratory Questionnaire.

Table 6. Comparison of rehabilitation-related indicators between the two groups (n=96)

Group	n	ICU stay time (means ± standard error of the mean)	Tracheal intubation rate, n (%)	28-day mortality, n (%)
Control one	48	7.86±2.23	14 (29.17)	8 (16.67)
Observation one	48	6.77±1.93	5 (10.42)	2 (4.17)
χ^2 or t		2.561	5.315	4.019
p-value		0.012	0.021	0.045

ICU, intensive care unit.

group. The tracheal intubation and 28-day mortality rates were significantly lower in the observation than in the control group ($P<0.05$; **Table 6**).

Discussion

In this study, we aimed to examine the clinical effects of HFNC oxygen therapy combined with naloxone on severe respiratory failure (SRF) in older adult patients. Patients with SRF cannot maintain normal gas exchange even in a well-oxygenated or resting state, causing hypoxia, secondary physiologic dysfunction, and metabolic disorders of the vital organs [12]. The pathogenesis is complex, and any lesion involving the respiratory tract, lung, thorax, CNS, or peripheral nerves can lead to respiratory failure and increased work of breathing, causing respiratory failure owing to respiratory muscle fatigue [13]. Non-invasive positive pressure ventilation combined with naloxone and other medications are the current clinical treatment for respiratory support. However, it cannot solve the problems of temperature or humidity, irritation from inhaled gas, or misaspiration. The overall efficacy is unsatisfactory, and resulting complications may worsen the QOL and prognosis of patients [14].

As a novel oxygen therapy modality, HFNC can provide a high gas flow rate, reduce the resistance of the upper respiratory tract and respiratory muscles, and eliminate the anatomic dead cavity of the upper airway better than the conventional oxygen inhalation method that is widely used to treat respiratory failure, CNS lesions, craniocerebral trauma, and poisoning [15, 16]. HFNC improves the prognosis of patients with SRF [17]. In this study, $PaCO_2$, RR, and pH of patients treated with HFNC oxygen therapy were lower after 2 and 3 days of treatment than those of patients treated with non-invasive positive pressure ventilation. Furthermore, PaO_2, PaO_2/FiO_2, and SaO_2 were higher after HFNC oxygen therapy than after non-invasive positive pressure ventilation. The ICU duration was significantly shorter with HFNC oxygen therapy than with non-invasive positive pressure ventilation. Finally, the SGRQ scores were lower after HFNC oxygen therapy than after non-invasive positive pressure ventilation. These results suggest that HFNC oxygen therapy when combined with naloxone for treating SRF in older adult patients, improved blood gas measurements and shortened the disease course. This is consistent with the findings of a previous study [18]. This is because the gas flow rate of HFNC is 50 L/min, which can effectively flush the invalid anatomical dead cavity of the nasopharynx, moisten the airway, soften sputum suppository, and promote sputum discharge. The warming and humidifying effects of HFNC can increase lung tissue compliance, reduce the work of breathing and oxygen consumption, and improve oxygen supply, thus improving respiratory failure [19, 20]. Therefore, HFNC oxygen therapy does not result in adverse effects, such as claustrophobia or abdominal distension. Moreover, compared to non-invasive positive pressure ventilation, HFNC oxygen therapy can improve the comfort of patients by promoting their ability to drink, eat, spit, and communicate, along with eliminating the facial pain caused by tight masks or fixed headbands [21].

Airway and systemic inflammatory responses are pathologic changes that occur in patients

with SRF. CC16 is a protective protein expressed at low levels in the inflammatory state. It results in increased lung cerebrospinal fluid barrier permeability and lung epithelial cell injury [22]. TNF-α is a proinflammatory cytokine produced by activated mononuclear macrophages that can damage endothelial cells, improve the function of phagocytes, and stimulate macrophages to release IL-1 [23]. IL-1 is a cytokine that stimulates the synthesis of colony factors, platelet growth factors, and other proinflammatory factors and is involved in the inflammatory response [24]. In this study, the post-treatment levels of TNF-α and IL-1 were lower in patients treated with HFNC oxygen therapy than in those treated with non-invasive positive pressure ventilation. Moreover, the CC16 levels were higher after HFNC oxygen therapy than those after non-invasive positive pressure ventilation. These results suggest that HFNC oxygen therapy combined with naloxone in older adult patients with SRF can better regulate the expressions of TNF-α, IL-1, and CC16 and reduce the degree of inflammatory response. This is a major mechanism underlying SRF treatment in older adults and is related to the ability of HFNC oxygen therapy in correcting hypoxia and promoting expectoration [25].

In this study, the tracheal intubation and 28-day mortality rates were lower after HFNC oxygen therapy than after non-invasive positive pressure ventilation, suggesting that HFNC oxygen therapy combined with naloxone in older adult patients with SRF can reduce the tracheal intubation and 28-day mortality rates, thereby improving patient prognosis. This is because HFNC oxygen therapy can improve respiratory failure and allow patients to resume spontaneous breathing, thereby avoiding the requirement for tracheal intubation during assisted breathing. Improvement in the inflammatory state of the patient can improve the disease prognosis. However, the sample size of this study was relatively small. Further studies involving larger patient populations are required to validate these findings.

In conclusion, HFNC oxygen therapy combined with naloxone to treat SRF in older adult patients can improve blood gas measurements, shorten the disease course, and reduce the tracheal intubation and 28-day mortality rates, possibly through regulation of TNF-α, IL-1, and CC16 expression.

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Disclosure of conflict of interest

None.

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