

Research Article

# Effect of High-Flow Nasal Cannula Oxygen Therapy with Awake Prone Position Ventilation vs. Supine Position Ventilation in Patients with Severe Pneumonia: A Quasi-Experimental Study

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## Abstract

**Objective:** This study aims to evaluate the effect of high-flow nasal cannula (HFNC) oxygen therapy combined with awake prone position ventilation (APPV) vs. supine position ventilation (SPV) in patients with severe pneumonia. **Methods:** This is a quasi-experimental study enrolled patients diagnosed with severe pneumonia from the Department of Respiratory and Critical Care Medicine of the Fourth People's Hospital of Zigong City between November 2021 and January 2023. The primary endpoint was the treatment effectiveness, and the secondary endpoints included 72 h respiratory rate oxygenation index, oxygenation index, procalcitonin within 72 h, C-reactive protein within 72 h and partial pressure of oxygen within 24 h, blood lactate within 24 h, total length of hospital stay, endotracheal intubation rate within 2 weeks, readmission rate within 6 weeks, mortality rate within 4 weeks and incidence of adverse events. **Results:** A total of 120 patients with severe pneumonia were enrolled, evenly divided with 60 patients receiving HFNC+APPV and the other 60 receiving HFNC+SPV. The HFNC+APPV group demonstrated higher efficacy (90.0% vs. 76.7%,  $P=0.040$ ) and shorter length of hospital stay (11.00(9.00,13.00) vs. 12.00(10.00,16.00),  $P=0.004$ ) compared to the HFNC+SPV group. There was no significant difference in ROX index, CRP, PCT, lactate, PO<sub>2</sub> and the onset of days, times of transferred to ICU within 1 week, times of transferred to ICU within 2 weeks, endotracheal intubation rate within 2 weeks, readmission rate within 6 weeks and mortality rate within 4 weeks between the HFNC+APPV group and HFNC+SPV group ( $P>0.05$ ). The generalized estimation equation showed that the OI index at 12h, 24h, 48h and 72h was significantly higher than that at 0h ( $P<0.001$ ), however, there was no significant difference in the change between HFNC+APPV group and HFNC+SPV group ( $P=0.604$ ). There was no significant difference in the rate of adverse events between the HFNC+APPV group and HFNC+SPV group ( $P>0.05$ ). **Conclusion:** The findings suggest that combining HFNC with APPV can enhance treatment efficacy and reduce hospitalization duration in severe pneumonia patients, offering valuable guidance for ventilation treatment positioning.

## Keywords

Severe Pneumonia, High-Flow Nasal Cannula, Awake Prone Position Ventilation, Supine Position Ventilation, Quasi-Experimental Study

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## 1. Introduction

Severe pneumonia is defined as a form of pneumonia that necessitates intensive care unit (ICU) treatment. [1] The overall incidence of severe pneumonia worldwide varies from 1 to 25 cases per 1000 individuals annually. [2] During the COVID-19 outbreak, patients with severe pneumonia have exhibited mortality rates of up to 40%. [3] Patients diagnosed with severe pneumonia usually received anti-infection, anti-shock treatment, nutritional support, sputum drainage and treatment of complications. [3] However, 5% of these individuals will need admission to the intensive care unit (ICU). [4] Mechanical ventilation, a lifesaving tool, helps stabilize patients with hypoxemic and hypercapnic respiratory failure, and decreases inspiratory work of breathing. [5] Invasive mechanical ventilation includes an endotracheal tube and a mechanical ventilator, as opposed to noninvasive ventilation in which the interface is a face mask. [6]

Transnasal high flow oxygen therapy (HFNC) is a non-invasive respiratory support technique employed in critically ill patients. HFNC delivers high flow gas of oxygen concentration, temperature and humidity, [7] which preserves the mucosal cilia clearance system's function, minimizes upper airway resistance, reduces breathing effort, and enhances ventilation function. It was reported that employing HFNC for severe pneumonia caused by COVID-19 could reduce ICU intubation rates and improve patient outcomes, posing minimal risk of caregiver contamination. [8]

Although supine position ventilation (SPV) has been widely utilized, studied revealed certain detrimental physiological alterations. [9] For instance, research indicates that abdominal cavity hydrostatic pressure can increase up to five folds compared to thoracic cavity pressure when in supine position. [9] Prone Position Ventilation (PPV) stands as an evidence-based therapy for individuals with moderate-to-severe respiratory dysfunction. [9] PPV ranks among the adjuvant treatments in the ICU, capable of enhancing oxygenation and rectifying hypoxemia in certain intubated patients. [10] Nevertheless, numerous non-invasive, conscious patients with severe pneumonia face challenges such as economic constraints or familial considerations, which make them miss out on PPV advantages. Fortunately, awake prone position ventilation (APPV) can be employed for spontaneously breathing patients undergoing non-invasive ventilation or HFNC outside the ICU, [11] which enhances oxygenation and reduces respiratory effort, especially when administered early to COVID-19 patients with acute respiratory failure. [12] However, currently, for patients diagnosed with severe pneumonia, the feasibility of employing a combined HFNC and APPV strategy remains inadequately documented.

This study aims to evaluate the clinical efficacy of combining HFNC and APPV vs. SPV in patients with severe pneumonia.

## 2. Materials and Methods

### 2.1. Study Design and Participants

This is a quasi-experimental study enrolled patients diagnosed with severe pneumonia at the Department of Respiratory and Intensive Care Medicine of the Fourth People's Hospital of Zigong City between November 2021 and January 2023. Inclusion criteria: 1) patients diagnosed as severe pneumonia in accordance with the US IDSA/ATS severe pneumonia criteria; [13] 2) conscious patients with an intact cough reflex; 3) patients with type I respiratory failure ( $\text{PaO}_2 \leq 100 \text{ mmHg}/\text{FiO}_2 < 300 \text{ mmHg}$ ); 4) patients with mild ventilatory dysfunction with blood gas analysis  $\text{pH} \geq 7.3$ . Exclusion criteria: 1) patients with unstable vital signs requiring emergency endotracheal intubation; 2) patients with impaired spontaneous breathing and unconsciousness; 3) patients with severe type I respiratory failure ( $\text{PaO}_2/\text{FiO}_2 < 60 \text{ mmHg}$ ); 4) patients with ventilatory dysfunction (blood gas analysis  $\text{pH} < 7.25$ ); 5) patients with inadequate airway protection and heightened aspiration risk; 6) patients with a history of nasal surgery or severe nasal obstruction, requiring open mouth breathing; 7) presence of active tuberculosis, pulmonary malignancy, non-infectious interstitial lung disease, acute pulmonary edema, pulmonary embolism, massive hemoptysis, or pneumothorax; 8) patients who recently received maxillofacial surgery, or with cervical, thoracic and lumbar fractures and intra-abdominal pressure. This study was under review by the ethics committee of the Fourth People's Hospital of Zigong City with ethics number: 2022-065. All patients provided written informed consent.

### 2.2. Intervention

The Heismus High Flow Transnasal Oxygen Therapy device, specifically the HUMID-BHR model, was used for all patients with severe pneumonia. The control group was administered HFNC+SPV, while the experimental group was administered HFNC+APPV.

The prone position timing strategy [14] involved elevating the patient's upper body using a pillow for APPV, typically selecting a timing of 1 hour after a meal for administering the prone ventilation treatment. A nasal plug catheter was used to connect the respiratory humidification device. The flow was set to 40 L/min (adjusted according to patient tolerance), with a temperature of 36 °C, and the oxygen concentration was regulated in accordance with  $\text{SpO}_2$  levels. The total daily prone time of patients in the observing group, based on their tolerance, was divided into five groups: <2 h, 2 h-6 h, 6 h-8 h, 8 h-12 h, and > 12 h.

### 2.3. Endpoints and Outcomes Measurement

The main endpoint of the study was the treatment efficacy. Secondary endpoints included 72 h respiratory rate oxygena-

tion (ROX) index, oxygenation index (OI), procalcitonin (PCT) within 72 h, C-reactive protein (CRP) within 72 h and partial pressure of oxygen (PO<sub>2</sub>) within 24 h, blood lactate within 24 h, total length of hospital stay, endotracheal intubation rate within 2 weeks, readmission rate within 6 weeks, mortality rate within 4 weeks and incidence of adverse events. Treatment efficacy is defined as a pulmonary CT scan showing a reduction of more than one-third in inflammatory lesions compared to pre-treatment, along with alleviation of coughing and wheezing symptoms. [15] Adverse events included postural hypotension, arrhythmia, fsophageal reflux, lung fibrosis at discharge. [12]

## 2.4. Statistical Analysis

The statistical analysis was performed using SPSS Statistics version 24.0 (IBM, Armonk, NY, USA). Normally distributed continuous data were presented as means  $\pm$  standard deviations (SD) and analyzed using Student's t-test. Non-normally distributed continuous data were presented as medians (interquartile range, IQR) and analyzed using the Wilcoxon rank-sum test. Categorical data were described as n (%) and examined using either the chi-square test or Fisher's exact test. Changes in ROX index, CRP, PCT, lactate, and PO<sub>2</sub> before and after intervention in both the HFNC+APPV and HFNC+SPV group were measured using Differences-in-Differences method. The changes in OI index before and after intervention in the HFNC+APPV and HFNC+SPV group were estimated using a generalized estimation equation

(GEM) model. Two-sided P-values  $<0.05$  were considered statistically significant.

## 3. Results

A total of 120 patients with severe pneumonia were enrolled, 60 patients were supported by HFNC+SPV, and the other 60 patients were supported by HFNC+APPV (Figure 1). The HFNC+APPV group and HFNC+SPV group exhibited comparable general characteristics, including age, sex, BMI, and basic medical history of type 2 diabetes, hypertension, pulmonary disease and heart disease (all  $P>0.05$ ) (Table 1). The HFNC+APPV group demonstrated higher efficacy (90.0% vs. 76.7%,  $P=0.040$ ) and shorter length of hospital stay (11.00 (9.00,13.00) vs. 12.00 (10.00,16.00),  $P=0.004$ ) compared to the HFNC+SPV group. There was no significant difference in ROX index, CRP, PCT, lactate, PO<sub>2</sub> and the onset of days, times of transferred to ICU within 1 week, times of transferred to ICU within 2 weeks, endotracheal intubation rate within 2 weeks, readmission rate within 6 weeks and mortality rate within 4 weeks between HFNC+APPV group and HFNC+SPV group ( $P>0.05$ ) (Table 2). The GEM model showed that the OI index at 12h, 24h, 48h and 72h was significantly higher than that at 0h ( $P<0.001$ ), however, there was no significant difference in the change between HFNC+APPV group and HFNC+SPV group ( $P=0.604$ ) (Table 3). There was no significant difference in the rate of adverse events between the HFNC+APPV group and the HFNC+SPV group ( $P>0.05$ , Table 4).

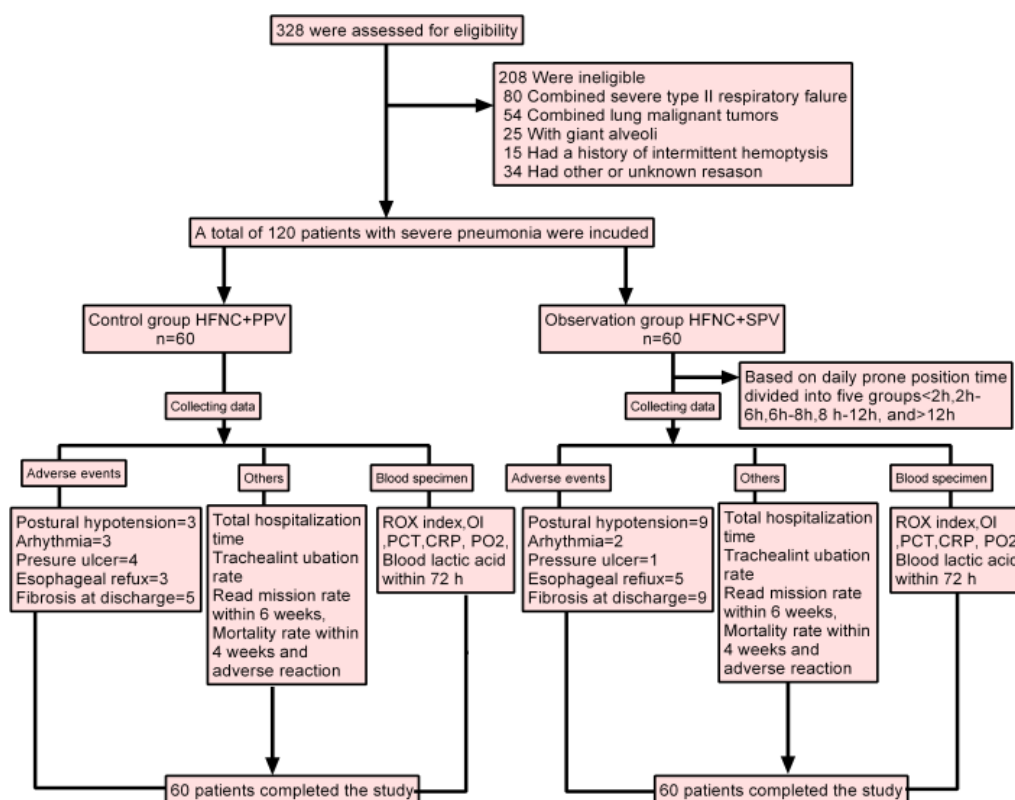


Figure 1. Flowchart.

**Table 1.** Basic characteristics.

Variable	HFNC+APPV group (n=60)	HFNC+SPV group (n=60)	P
Sex, male, n/%	23 (38.3%)	22 (36.7%)	0.850
Age, Mean $\pm$ SD	63.68 $\pm$ 6.15	63.55 $\pm$ 6.07	0.905
BMI, kg/m <sup>2</sup> , Mean $\pm$ SD	19.93 $\pm$ 1.77	19.79 $\pm$ 1.55	0.643
Type 2 diabetes, n/%	22 (36.7%)	14 (23.3%)	0.111
Hypertension, n/%	27 (45.0%)	26 (43.3%)	0.854
History of the underlying pulmonary disease, n/%	22 (36.7%)	25 (41.7%)	0.575
History of Heart Disease, n/%	16 (26.7%)	18 (30.0%)	0.685

Note: BMI: body mass index.

**Table 2.** Outcomes.

Variable	HFNC+APPV group (n=60)	HFNC+SPV group (n=60)	P
Efficacy, n/%	54 (90.0%)	46 (76.7%)	0.040
ROX index' Mean $\pm$ SD			0.305
0h	4.89 $\pm$ 0.43	4.89 $\pm$ 0.22	
72h	5.50 $\pm$ 0.65	5.24 $\pm$ 0.46	
CRP' Mean $\pm$ SD			0.478
0h	55.81 $\pm$ 39.87	43.18 $\pm$ 21.14	
72h	25.76 $\pm$ 32.49	27.65 $\pm$ 27.97	
PCT' Mean $\pm$ SD			0.916
0h	1.72 $\pm$ 1.24	2.19 $\pm$ 1.20	
72h	1.02 $\pm$ 1.61	1.46 $\pm$ 1.52	
Lactate' Mean $\pm$ SD			0.604
0h	4.62 $\pm$ 2.26	3.43 $\pm$ 1.75	
24h	2.77 $\pm$ 2.84	2.76 $\pm$ 3.49	
PO2, Mean $\pm$ SD			0.454
0h	76.17 $\pm$ 4.68	77.62 $\pm$ 4.01	
24h	84.02 $\pm$ 5.06	82.78 $\pm$ 4.14	
The onset of days, medians (IQR)	5.00 (4.00,6.00)	5.00 (4.00,5.00)	0.681
Length of hospital stay (days), medians (IQR)	11.00 (9.00,13.00)	12.00 (10.00,16.00)	0.004
Times of transferred to ICU within 2 weeks, n/%	6 (10.0%)	8 (13.3%)	0.570
Times of transferred to ICU within 1 week, n/%	3 (5.0%)	2 (3.3%)	1.000
Endotracheal intubation rate within 2 weeks, n/%	3 (5.0%)	0 (0.0%)	0.245
Readmission rate within 6 weeks, n/%	4 (7.4%)	9 (16.4%)	0.149
Mortality rate within 4 weeks, n/%	4 (6.7)	5 (8.3%)	1.000

Note: Efficacy is defined as pulmonary CT showing that inflammatory lesions are absorbed more than 1/3 compared to before treatment, and coughing and wheezing symptoms are relieved.

**Table 3.** Changes in OI index at 72 hours of admission between the two groups.

group	0h	12h	24h	48h	72h
HFNC+APPV group	252.89±34.86	284.18±39.00*	315.96±49.81*	344.41±56.24*	370.55±64.30*
HFNC+SPV group	263.06±21.04	285.68±26.79*	311.41±37.18*	338.58±45.06*	364.27±57.90*
P time	-	<0.001	<0.001	<0.001	<0.001
P group	0.604				

Note: Compared with the same group at time 0 h, \*P <0.05; comparing the same time point with the HFNC+SPV group, #P <0.05.

**Table 4.** Adverse events.

variable	HFNC+APPV group (n=60)	HFNC+SPV group (n=60)	P
Pressure ulcer	1 (1.7%)	4 (6.7%)	0.361
Postural hypotension	9 (15.0%)	3 (5.0%)	0.068
Arrhythmia	2 (3.3%)	3 (5.0%)	0.648
Esophageal reflux	5 (8.3%)	3 (5.0%)	0.714
Fibrosis at discharge	9 (15.0%)	5 (8.3%)	0.237

## 4. Discussion

The study showed that the HFNC+APPV treatment displayed significantly higher efficacy and shorter length of hospital stay compared to the HFNC+SPV treatment, which provides valuable insights into clinical practices in respiratory therapy of patients with severe pneumonia.

The findings in this present study are consistent with previous studies on the efficacy of APPV and HFNC, which have reported enhanced oxygenation alongside reduced respiratory effort when administered promptly to COVID-19 patients experiencing acute respiratory failure. [16] In both groups of the current study, HFNC was employed, which improves oxygenation by delivering humidified oxygen at a high flow rate, enabling alveolar FiO<sub>2</sub> to attain a predetermined level. Numerous studies have demonstrated that APPV reduced mortality among patients with moderate to severe acute respiratory distress syndrome (ARDS) who necessitate intubation and mechanical ventilation. [16] Kaur et al. found that early initiation of APPV (<24 h with HFNC) improves 28-day survival for cases of acute hypoxic respiratory failure arising from COVID-19. [17] A meta-analysis conducted by Chua et al. indicated that PPV led to an enhanced PaO<sub>2</sub>/FiO<sub>2</sub> ratio and superior SpO<sub>2</sub> compared to SPV in COVID-19 patients. [10] The improvement in patients receiving APPV might be resulted from the advantages that APPV enhances oxygenation through improved aeration and ventilation in the lung's pre-

dominantly vertebral regions, which receive the majority of pulmonary blood flow, which reduces intra-pulmonary shunting in these regions. [18] Likewise, prone ventilation in the HFNC+APPV group of this study could potentially enhance blood flow distribution in the lungs, elevate the oxygen content in the gravity-dependent region of the lungs, and consequently promote a coordinated ventilation-to-perfusion ratio.

Compared to APPV, SPV appears to have more disadvantages. A study showed that in the supine position, the abdominal cavity hydrostatic pressure can be as much as five times higher than that in the thoracic cavity. [19] The highest intra-abdominal pressures in supine decubitus correspond to the dorsal regions, where pressure is inexorably transmitted to the pleural space, generating extrinsic compression to the postero-basal pulmonary region. [9] However, a study investigated the long-term outcomes in survivors of acute respiratory distress syndrome ventilated in supine or prone position also reported that no differences in pulmonary function or quality of life were observed in patients treated in prone versus supine positions, [20] which might be resulted from the small sample size and the various severity of pulmonary function impairment.

Although the treatment efficacy of HFNC+APPV is significantly higher than that of the HFNC+SPV group, but the ICU transfer rate within 2 weeks, intubation rate, mortality rate within 4 weeks, and readmission rate within 6 weeks exhibited no statistically significant disparities between the HFNC+APPV group and the HFNC+SPV group in this study.



Parallel to our results, a multicenter randomized clinical trial by Jacob Rosen et al. showed that APPV prolonged the duration of prone positioning when compared to SPV, but had no effect on intubation rates and 28-day mortality in patients with moderate to severe hypoxic respiratory failure. [21] A prospective multicenter study by Ferrando C et al. assessed the potential advantages of combining HFNC with APPV to prevent intubation in patients with COVID-19, but ultimately concluded that this HFNC+APPV did not reduce the risk of intubation. [22] Additionally, the readmission rate was evaluated in this present study for the first time. The results showed that within 6 weeks after discharge, 4 patients in the HFNC+APPV group and 6 patients in the HFNC+SPV group were readmitted. The possibility of readmission due to other pulmonary factors could not be entirely ruled out.

ROX, defined as the ratio of oxygen saturation, has emerged as a predictive marker for patients likely to respond positively to HFNO therapy, aiding clinicians in determining the appropriate timing for intubation. [23] A study investigating the effect of APPV on ROX Index in critically-ill patients with respiratory failure due to COVID-19 showed that ROX index was improved by APPV only in non-intubated patients but not in intubated patients. [24] However, our findings demonstrated an increase of the ROX index in both the experimental group and the HFNC+SPV group at the 72 h. In this present study, no significant difference in ROX index was observed between the HFNC+APPV group and HFNC+SPV group, implying that APPV and SPV could not affect patients' ROX index to HFNC therapy. Moreover, in the present study, no significant differences in CRP and PCT at 72 h between the HFNC+APPV group and HFNC+SPV group was observed, suggesting that APPV treatment might not be more powerful in improving the inflammatory response when compared to SPV. Additionally, no significant differences in blood lactate level, PO<sub>2</sub> at 24 h and OI index emerged between the HFNC+APPV and HFNC+SPV groups, demonstrating that the O<sub>2</sub> delivery was not significantly affected by the position when receiving ventilation. Interestingly, the length of hospital stay in the HFNC+APPV group was significantly shorter than that of the HFNC+SPV group, which might be resulted from the advantages brought by spontaneous breathing during APPV which enhances gas exchange, lowers inspiratory force and pulmonary pressure, and indirectly mitigates the systemic inflammatory response.

Although previous study have documented the adverse effects of APPV, such as postural hypotension, arrhythmias, ulcers, and esophageal reflux, no statistical significance was observed in the rate of adverse effects between the HFNC+APPV group and HFNC+SPV group in this study. A randomized clinical trial also showed the absence of any serious adverse events in both the prone positioning group and HFNC+SPV group. [25] Although the findings of our current study indicated that certain patients developed pulmonary interstitial fibrosis, however, no statistical difference was

observed in this aspect between the two groups. This phenomenon could be attributed to the higher incidence of pulmonary interstitial fibrosis among COVID-19 patients compared to the general population.

There were still several limitations in this study. First, some patients had to discontinue the study due to their inability to tolerate prolonged prone positioning, lowering the study's statistical power to detect variations between the groups. Second, the partial unblinding elevated the potential for bias. Third, the study comprised of patients with moderate to severe respiratory failure, potentially limiting the applicability of findings in this study to patients with milder respiratory distress. Fourth, the study predominantly delved into the severity of respiratory failure, omitted the etiological heterogeneity. For instance, some patients presented bacterial pneumonia while a majority contracted viral pneumonia (e.g., COVID-19), and disparities in treatment options hindered efficacy assessment. Fifth, this investigation is a single-center study with a relatively small sample size. Future randomized controlled trial with larger sample were needed to validate the results.

## 5. Conclusion

In conclusion, the utilization of HFNC in conjunction with APPV demonstrates the potential to increase the efficacy of HFNC, and reduce the duration of hospitalization in individuals with severe pneumonia, which provides reliable theoretical guidance for the choice of ventilation treatment position for patients with severe pneumonia.

## Abbreviations

HFNC	High-flow Nasal Cannula
APPV	Awake Prone Position Ventilation
SPV	Supine Position Ventilation
ICU	Intensive Care Unit
PPV	Prone Position Ventilation
ROX	Rate Oxygenation
OI	Oxygenation Index
PCT	Procalcitonin
ARDS	Acute Respiratory Distress Syndrome

## Acknowledgments

Not applicable.

## Author Contributions

**Aibo Zheng:** Conceptualization, Data curation, Software, Writing – original draft

**Kai Sun:** Investigation, Project administration, Resources, Writing – review & editing

**Shengjun Ma:** Data curation, Formal Analysis, Software

**Ping Liu:** Supervision, Validation

**Yibo Shen:** Formal Analysis, Methodology

**Li Gu:** Methodology, Validation

**Juan Peng:** Data curation, Visualization

## Declarations

## Ethics Approval and Consent to Participate

The study was carried out after the protocol was approved by the ethics committee of the Fourth People's Hospital of Zigong City (2022-065). I confirm that all methods were performed in accordance with the relevant guidelines. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and informed consent was obtained from all participants.

## Consent for Publication

Not applicable.

## Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

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## Conflicts of Interest

The authors declare that they have no competing interests.

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