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A retrospective study to predict failure of high-flow oxygen therapy for acute hypoxic respiratory failure

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Abstract

Objective This study aimed to analyze the characteristics of patients who fail high-flow nasal cannula(HFNC) therapy for acute hypoxemic respiratory failure(AHRF) and to identify predictors of treatment failure.

Methods This single-center, retrospective, observational study analyzed clinical data from 388 patients with AHRF. Patients were divided into two groups: the HFNC success group (HFNC-S, $n=256$) and the HFNC failure group (HFNC-F, $n=132$). The primary endpoint was the need for escalation of respiratory support to tracheal intubation in the enrolled patients. The demographic data, laboratory tests, blood gas analysis data, CT severity scores, and disease severity scores were analysed to determine the difference between patients who were successful and those who failed HFNC treatment. Univariate and multivariate logistic regression models were used to assess potential predictors of failure of HFNC for patients with acute hypoxaemic respiratory failure.

Results The mean age of patients enrolled was 67.97 ± 14.40 years. The HFNC-F group had significantly higher PSI(Pneumonia Severity Index) score, CURB(Confusion, Urea, Respiratory Rate, Blood Pressure, and Age)-65 score, CPIS(Clinical Pulmonary Infection Score) score, CT score and SOFA(Sequential Organ Failure Assessment) scores compared to the HFNC-S group. Within 12 h of the initiation of treatment, the HFNC-F group exhibited significantly lower oxygen saturation index (PaO2/FiO2) and significantly higher respiratory rate. Additionally, the HFNC-F group exhibited significantly higher levels of C-reactive protein (CRP), platelet count (PLT), D-dimer, interleukin-10 (IL-10), total bilirubin (TB) and creatinine (CB), but lower albumin levels.

Multivariate analysis identified CT score, SOFA score, interleukin-1β (IL-1β), and albumin as independent predictors of HFNC failure.

Conclusion HFNC is effective for treating AHRF. CT score, SOFA score, IL-1β, and albumin are independent predictors of HFNC failure.

Keywords Failure of high-flow oxygen therapy, Acute hypoxic respiratory failure, A retrospective study

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Introduction

High-flow nasal cannula (HFNC) oxygen therapy is a novel and effective non-invasive respiratory support modality. HFNC is adept at delivering a stable and precise amount of inspired oxygen, thereby increasing the arterial blood partial pressure of oxygen. Furthermore, HFNC has the advantage of delivering heated and humidified gases, which help to activate the mucus cilia in the airway and facilitate sputum clearance [1, 2].

HFNC oxygen therapy delivers heated and humidified gas at high flow rates, providing multiple physiological benefits that collectively improve respiratory function. Key mechanisms of action include: 1) reduction of inspiratory effort through washout of nasopharyngeal dead space [3]; 2) improvement of lung volumes and compliance via generation of low-level positive airway pressure (typically 2–5 cmH2O) [4]; 3) enhancement of oxygenation efficiency by decreasing anatomical dead space through high-flow gas delivery; and 4) reduction in respiratory rate and work of breathing through optimal matching of inspiratory flow demands [5]. These synergistic physiological effects contribute to HFNC's demonstrated capacity to prevent clinical deterioration, thereby reducing the need for escalation to more invasive respiratory support modalities such as non-invasive or mechanical ventilation [6]. The application of positive end-expiratory pressure (PEEP) generated by HFNC results in an increase in functional residual capacity, thereby conferring upon the patient a degree of respiratory function that is comparable to that achieved through non-invasive ventilation. This device is particularly suited to patients with acute hypoxaemic respiratory failure (AHRF).

AHRF is a life-threatening condition prevalent in emergency intensive care units (EICUs). In the absence of treatment, patients with AHRF are at a markedly elevated risk of mortality. The primary strategies for the prevention of acute hypoxaemic respiratory failure from progressing to the point where invasive mechanical ventilation is required are non-invasive respiratory support methods, including non-invasive ventilation (NIV), continuous positive airway pressure (CPAP) and high flow nasal oxygen (HFNC). Among these, HFNC therapy is becoming increasingly popular in the treatment of ARF, and HFNC has unique advantages in improving acute hypoxaemic respiratory failure [7].

HFNC is an effective and safe alternative in elderly patients with AHRF, refractory to treatment with conventional oxygen therapy and/or in tolerant to NIV or CPAP and without criteria for admission to ICU [8]. Even in obese adult critically ill patients with moderate risk of intubation failure, the reintubation rate of HFNC is significantly lower than that of NIV [9]. The RENOVATE trial showed that in most subgroups of acute respiratory failure, high flow nasal oxygen (HFNO) did not have a significant advantage over non-invasive ventilation (NIV) (or 1.07, 95% CI 0.81–1.39) in preventing tracheal intubation or 7-day mortality [10].

Despite HFNC's demonstrated benefits, predictive factors for treatment failure in AHRF patients remain clinically under characterized. This study aimed to compare clinical characteristics between HFNC success and failure groups in acute hypoxemic respiratory failure, and identify independent predictors of HFNC failure to optimize treatment protocols.

Materials and methods

Study population and inclusion criteria

This study included consecutive adult patients admitted to the emergency department of Zhongshan Hospital, Fudan University (January–December 2023) with radiologically and clinically confirmed pneumonia, complicated by acute hypoxemic respiratory failure requiring HFNC. Pneumonia severity was assessed using PSI and CURB-65 scores at enrollment. All 388 patients underwent standardized RT-PCR testing for SARS-CoV-2.

The patients were divided into two groups: the HFNC treatment success group (HFNC-S group, 256) and the HFNC treatment failure group (HFNC-F group, 132). Both groups of patients received comprehensive nursing interventions.

Inclusion criteria were as follows: patients aged ≥ 14 years met the following criteria: 1) Acute respiratory failure, known clinical symptoms, and new or worsening respiratory symptoms within one week; 2) New inflammatory infiltrates in the lungs detected by chest radiograph or chest CT; and 3) Arterial blood gas analysis suggesting that PaO2 ≤ 60 mm Hg and the ratio of PaO2 to FIO2 < 300. The following exclusion criteria were applied: 1) Endotracheal intubation or imminent need for endotracheal intubation; 2) Pulmonary oedema due to heart failure; 3) Exacerbation of asthma or chronic lung disease; 4) Haemodynamic instability (mean arterial pressure < 65 mmHg, or use of vasoactive drugs); 5) Incomplete recording of relevant variables.

Study design

This retrospective cohort study analyzed electronic medical records of consecutively admitted patients meeting inclusion criteria. Data were extracted from the hospital's database and manually verified by two independent researchers. The retrospective design allowed standardized collection of: The laboratory values; High-resolution physiological monitoring data; Unified endpoint adjudication by blinded clinicians. Prior to multivariate logistic regression, bivariate analyses were performed to identify

variables significantly associated with HFNC failure ($p < 0.05$). Potential collinearity among overlapping clinical scores (e.g., PSI, CURB-65, SOFA) was assessed using variance inflation factors (VIF), with all values < 5 indicating acceptable multicollinearity. Sensitivity analyses via stepwise regression confirmed the robustness of the final model.

Settings for HFNC

The enrolled patients were provided with high-concentration oxygen therapy via a Midray ventilator (SV350, Shenzhen, China) utilising the high-flow oxygen therapy mode. The initial airflow was set at 30–50 L/min, and the FIO2 of the enrolled patients was adjusted periodically so that the peripheral capillary oxygen saturation (SpO2) was maintained between 92 and 98%. It was permitted to switch treatments, namely intubation or receipt of a non-specified intervention (CPAP or HFNC), only after the predefined intubation criteria had been met.

HFNC failure criteria: a. The criteria for intubation were predefined as follows: 1) Haemodynamic instability; 2) Signs of worsening respiratory failure (defined by at least two of the following criteria): a respiratory rate of more than 40 breaths per minute, pronounced assisted respiratory muscle activity or chest and abdominal paradoxical respiration, the presence of large amounts of tracheal secretions, poor airway protection, acidosis (pH less than 7.35), SpO2 less than 90% for more than 5 min, and a progressive elevation of PaCO2. b. Mortality within 48 h of HFNC initiation without intubation.

Clinical characteristics, laboratory parameters, blood gas analysis, and CT scores

Laboratory and imaging data were collected at the commencement of the use of high-flow nasal cannula (HFNC) therapy. The data were collected by reviewing the electronic medical records of the enrolled patients. This entailed the collection of demographic characteristics (age and gender), length of stay, etiology, underlying disease, haematology laboratory parameters at admission, PSI score, CURB-65 score, CPIS score, CT score and SOFA score. Pro-inflammatory markers, coagulation markers, and organ function assessment indices were evaluated at the time of patient admission to the intensive care unit. The primary outcome was defined as the failure of HFNC, which necessitated the escalation of respiratory support (including non-invasive or invasive mechanical ventilation). A blood gas analysis was conducted on 1 mL of blood drawn from the patient's radial artery using a Roche Cobas B123 blood gas analyser. The respiratory rate (RR), SpO2, oxygenation index (PaO2/FiO2), and PCO2 values were collected from all patients at 1, 6, 12, 24, 48, and 72 h after treatment.

Chest computed tomography (CT) score: All enrolled patients underwent a chest CT scan on admission and were assessed for the severity of the CT scan, including bilateral lung involvement, the presence of ground-glass opacities, comorbidities, lobular septal thickening, pleural effusion, and lymph node enlargement. Independent scoring by 2 radiologists with ≥ 5 years of experience. The improved version of the Radiographic Assessment of Lung Edema (RALE) Score is mainly used to quantify the imaging severity of pneumonia. Each lung lobe was scored on a scale of 0 to 5, with 0 representing no observed changes and 5 representing the most severe observed changes. The maximum possible score was 25, with each lobe of the right lung and each lobe of the left lung being scored separately. The trial was conducted in accordance with the principles set forth in the Declaration of Helsinki. The study protocol was approved by the Clinical Research Ethics Committee of Zhongshan Hospital, Fudan University (Approval No. B2021-542R), and written informed consent was obtained from all patients before their participation.

Statistical analysis

The statistical analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago), a software package designed for the analysis of quantitative data. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Non-normally distributed continuous variables are presented as median and interquartile range (Q1-Q3). Continuous variables were compared between independent groups using the Wilcoxon rank sum test, while paired samples were analysed using the paired Wilcoxon rank sum test. Comparisons of categorical variables were conducted using either the chi-square test or Fisher's exact test. Cox proportional hazards models were employed to assess the associations between the outcomes and predictor variables. Hazard ratios (HR) and their 95% confidence intervals (CI) were reported to quantify the magnitude and direction of the association. All statistical tests were conducted with a two-tailed hypothesis and a significance threshold of 0.05. Receiver operating characteristic (ROC) curves were employed to ascertain the optimal cut-offs, sensitivity, and specificity, with the areas under the ROC curves (AUCs) subsequently calculated. No estimates were made for missing data.

Results

Comparison of general information between HFNC-S group and HFNC-F group

A total of 400 patients presenting with acute hypoxaemic respiratory failure in the emergency care unit of Zhongshan Hospital were included in the study between

1 January 2022 and 31 December 2023. Twelve patients were excluded according to the exclusion criteria, and 388 patients were finally analysed (Fig. 1). Of the 388 patients initially treated with oxygen via HFNC, 132 (34%) failed high-flow oxygen therapy and were subsequently treated with IMV or died. The enrolled patients were predominantly male ($n=284$, 73.20%), with a mean age of (67.97 ± 14.40) years. However, no significant differences were found between the two groups. The prevalence of COVID-19 infections was 53.13% in the patients in the HFNC-treatment failure group and 48.48% in the success group.

This study included a total of 338 patients. The mean ROX index was 5.9487 ± 2.6762 overall. The HFNC-F group showed a significantly lower ROX index (4.7283 ± 1.8895) compared to the HFNC-S group (6.5779 ± 2.8139), with this difference reaching statistical significance.

The majority of patients in both groups exhibited underlying medical conditions, including hypertension, chronic heart disease, diabetes mellitus, COPD, and emphysema. However, no significant differences were observed between the two groups. The PSI score, CURB-65 score and CPIS score, the 0-h CT score and the SOFA score were found to be significantly higher in the HFNC failure group than in the HFNC success group (Table 1).

Comparison of blood gas analyses between HFNC-S group and HFNC-F group

A comparison of the blood gas analyses of the HFNC-failure group at 0, 6 and 12 h from the beginning of the treatment with those of the success group revealed that the respiratory rate was significantly higher in the failure group, while the oxygen and index were significantly lower (Supplementary Table 1). However, there was no significant difference in PCO2 and SpO2. However, at 24, 48 and 72 h of HFNC treatment, there were no significant differences in respiratory rate, oxygen and index, PCO2 and SpO2 between the two groups.

The early differences in PaO_2/FiO_2(0-12 h) likely reflect initial disease severity stratification, while later convergence (24-72 h) may indicate either: therapeutic stabilization in surviving HFNC-F patients; attrition of severe cases through intubation/mortality; delayed treatment effects in initially non-responsive patients; this pattern aligns with the known 48-72 h critical window for HFNC outcome determination.

Comparison of laboratory tests between HFNC-S group and HFNC-F group

In terms of infection indexes, the white blood cell count, neutrophil percentage and PCT of patients in the HFNC-failure group were generally elevated. In addition, the C-reactive protein in the failure group was significantly higher than that in the success group.

In terms of coagulation indexes, there was no significant difference in PT, INR, TT, APTT and Fib between the two groups. However, D-Dimer in the failure group was significantly higher than that in the success group, and platelet count was significantly lower than that in the success group.

Additionally, TNF-α, IL-1β, IL-2, IL-6, and IL-8 were generally elevated in patients in the HFNC failure group, with IL-10 concentrations significantly higher in the failure group.

With regard to organ function, total and conjugated bilirubin were found to be significantly higher in the HFNC treatment failure group than in the success group

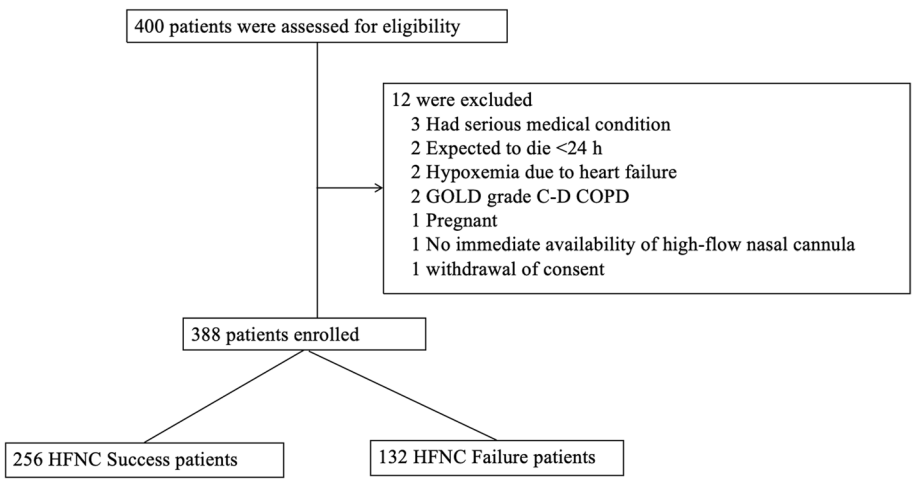

Fig. 1 Flow diagram of detailed information on allocation and the excluded patients

Table 1 Baseline demographic characteristic of the patients, according to study

Characteristic	All Patients ($n=388$)	HFNC Success Group ($n=256$)	HFNC Failure Group ($n=132$)	p
Age (years, mean ± SD)	67.97 ± 14.40	66.84 ± 13.83	70.15 ± 15.44	0.286
Gender				
Male (n, %)	284, 73.20%	188, 73.43%	96, 72.73%	0.941
Female (n, %)	104, 26.80%	68, 26.57%	36, 27.27%	
Comorbidities and risk factors				
Hypertension (n, %)	244, 62.89%	168, 65.63%	76, 57.58%	0.442
Chronic Cardiac disease (n, %)	116, 27.84%	56, 21.88%	20, 15.15%	0.474
Diabetes mellitus (n, %)	120, 30.93%	80, 31.25%	40, 30.30%	0.925
COPD (n, %)	20, 0.52%	12, 4.69%	8, 6.06%	0.775
Emphysema(n, %)	20, 0.52%	8, 3.13%	8, 6.06%	0.236
Current smoker	44, 11.34%	28, 10.94%	16, 12.12%	0.863
COVID 19	200, 51.55%	136, 53.13%	64, 48.48%	0.669
Time since symptom onset (d)	14.25 ± 13.22	13.13 ± 11.17	16.42 ± 16.47	0.246
Whether the host is immunosuppressed (n, %)	27, 27.84%	14, 21.88%	13, 39.39%	0.069
ROX index	5.9487 ± 2.6762	6.5779 ± 2.8139	6.5779 ± 2.8139	0.001
PSI score				0.001
I (n, %)	3(3.09%)	3(4.69%)	0	
II (n, %)	10(10.31%)	9(14.06%)	1(3.03%)	
III (n, %)	25(25.77)	20(31.25%)	5(15.15%)	
IV (n, %)	38(39.18%)	23(35.94%)	15(45.45%)	
V (n, %)	21(21.65%)	9(14.06%)	12(36.36%)	
CURB-65	1.577 ± 0.945	1.422 ± 0.956	1.879 ± 0.857	0.023
CPIS Score	1.879 ± 0.857	4.578 ± 1.434	5.242 ± 1.480	0.035
CT score				
0 h CT score	12.28 ± 4.132	11.52 ± 4.136	13.81 ± 3.736	0.011
1 week CT score	11.53 ± 4.795	11.27 ± 5.196	11.96 ± 4.118	0.574
APACHE II score	13.64 ± 6.327	12.71 ± 6.474	15.18 ± 5.844	0.076
SOFA score	4.614 ± 2.826	3.946 ± 2.383	5.727 ± 3.175	0.004
Glucocorticoid (n, %)	80, 82.47%	51, 79.69%	29, 87.88%	0.32

(Table 2 and Supplementary Table 2)). In contrast, albumin levels were significantly lower in the failure group.

HFNC treatment failure prediction model

A multivariate regression analysis was conducted, incorporating the PSI score, CURB-65 score, CPIS score, 0-h CT score, SOFA score, CRP, PLT, D-dimer, TNF-α, IL-1β, IL-2, IL-6, IL-8, L10, TB, CB and albumin. The results of the multivariate regression analyses indicated that the CT score (OR: 1.622, 95% CI: 1.117–2.355), SOFA score (OR: 1.868, 95% CI: 1.087–3.209), IL1β (OR: 0.041, 95% CI: 0.738–0.994), and albumin (OR: 0.034, 95% CI: 0.479–0.972) were all independent predictors of oxygen treatment failure ($P<0.05$) (Fig. 2).

ROC curve analysis was employed to evaluate the predictive value of CT score, SOFA score, IL1β, and albumin in relation to HFNC failure. The area under the curve for albumin was 0.852 (95% CI 0.777–0.928, $p<0.001$), and for IL-1β was 0.807 (95% CI 0.696–0.919, $p<0.001$), the area under the curve for SOFA score was 0.853 (95% CI 0.775–0.930, $p<0.001$), and the area under the curve for CT score was 0.876 (95% CI 0.810 -0.942, $p<0.001$). The optimal cut-off value for albumin was 29.5, with a sensitivity of 85.9% and a specificity of 69.7%. The optimal cut-off value for IL-1β was 14.7, with a sensitivity of 69.7% and a specificity of 99.6%. The optimal cut-off value for the SOFA score was 4.5, with a sensitivity of 78.8% and a specificity of 79.7%. Finally, the optimal cut-off value for the CT score was 12.5, with a sensitivity of 93.9% and a specificity of 75.0% (Fig. 3).

Discussion

Acute hypoxaemic respiratory failure and HFNC efficacy. Acute hypoxaemic respiratory failure remains a significant cause of mortality in EICU patients. While HFNC demonstrates physiological advantages through its ability

Table 2 Results of laboratory tests

	All Patients ($n=388$) Mean ± SD	HFNC Success Group ($n=256$) Mean ± SD	HFNC Failure Group ($n=132$) Mean ± SD	reference value	*p*
WBC (*10^9/L)	10.14 ± 6.140	10.57 ± 6.561	9.294 ± 5.218	3.5–9.5	0.335
N (%)	85.57 ± 13.16	85.41 ± 14.22	85.93 ± 10.66	40–75	0.864
CRP (mg/L)	94.43 ± 83.63	83.31 ± 87.62	116.3 ± 71.46	0–10	0.029
PCT (ng/mL)	3.639 ± 10.50	3.745 ± 12.14	3.430 ± 6.311	< 0.5	0.893
L (%)	8.666 ± 10.05	9.520 ± 11.99	7.039 ± 4.214	20–50	0.268
ESR (mm/h)	57.00 ± 35.72	56.74 ± 33.58	57.47 ± 40.52	0–20	0.951
Hb (g/L)	111.98 ± 26.44	114.44 ± 26.85	107.21 ± 25.32	130–175	0.204
PLT (*10^9/L)	193.14 ± 97.10	211.86 ± 100.9	156.85 ± 78.62	125–350	0.008
Lac (mmol/L)	3.240 ± 3.471	3.072 ± 2.877	3.631 ± 4.649	0.5–1.7	0.572
PT (s)	15.37 ± 13.91	15.43 ± 16.95	15.26 ± 4.853	10–13	0.954
INR	1.314 ± 1.223	1.317 ± 1.488	1.307 ± 0.441	0.5–1.2	0.971
TT (s)	15.87 ± 2.096	15.73 ± 1.345	16.15 ± 3.042	14–21	0.359
APTT (s)	31.06 ± 8.879	30.06 ± 6.954	32.91 ± 11.53	25–31.3	0.138
Fib (mg/dL)	498.67 ± 220.30	495.03 ± 234.84	505.40 ± 193.83	200–400	0.829
D-Dimer (mg/L)	6.495 ± 10.33	5.135 ± 9.412	9.010 ± 11.58	0–0.8	0.033
TNFa (pg/mL)	28.70 ± 107.2	15.99 ± 18.58	55.48 ± 186.5	< 8.1	0.109
IL-1b (pg/mL)	16.55 ± 67.13	9.707 ± 14.02	30.47 ± 115.3	< 5.0	0.174
IL-2 (pg/mL)	1420.57 ± 1459.25	1237.29 ± 1182.11	1806.79 ± 1884.86	223–710	0.089
IL-6 (pg/mL)	99.97 ± 230.45	69.64 ± 189.90	159.61 ± 288.94	< 3.4	0.082
IL-8 (pg/mL)	148.83 ± 801.16	47.83 ± 67.77	361.64 ± 1401.90	< 6.2	0.088
IL-10 (pg/mL)	36.59 ± 150.47	11.84 ± 21.87	88.73 ± 258.72	< 9.1	0.025
TB (umol/L)	13.57 ± 12.18	11.49 ± 9.256	17.53 ± 15.80	3.4–20.4	0.02
CB (umol/L)	5.981 ± 8.658	4.184 ± 3.825	9.412 ± 13.25	0–6.8	0.004
ALT (U/L)	123.90 ± 433.43	127.97 ± 451.23	116.12 ± 403.89	9–50	0.9
AST (U/L)	177.43 ± 761.73	216.56 ± 921.74	102.73 ± 260.21	15–40	0.49
LDH (U/L)	606.47 ± 1143.30	633.97 ± 1375.09	554.82 ± 480.66	109–245	0.75
Albumin (g/L)	32.79 ± 4.864	33.76 ± 4.848	30.94 ± 4.394	35–55	0.006
Creatinine(umol/L)	153.37 ± 203.33	148.38 ± 209.46	162.61 ± 194.31	44–115	0.748
Urea(umol/L)	12.52 ± 10.75	11.24 ± 9.431	14.89 ± 12.66	2.9–8.2	0.117
cTNT (ng/mL)	0.0688 ± 0.181	0.0798 ± 0.2207	0.048 ± 0.0431	< 0.014	0.424
proBNP(pg/mL)	3730.02 ± 7059.32	3502.83 ± 6590.11	4163.12 ± 7971.34	1–100	0.671

Abbreviations: *HFNC* high-flow nasal cannula, *SD* standard deviation, *WBC* white blood cell, *N(%)* Neutriphil percentage, *CRP* C-reactive protein, *PCT* procalcitonin, *L(%)* lymphocyte percentage, *ESR* Erythrocyte sedimentation rate, *Hb* hemoglobin, *PLT* platelet, *Lac* Lactic acid, *INR* international normalized ratio, *TT* thrombin time, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *TNFα* tumor necrosis factor, *IL-1β* interleukin β, *IL-6* interleukin 6, *IL-8* interleukin 8, *IL-10* interleukin-10, *TB* total bilirubin, *CB* conjuged bilirubin, *ALT* alanine transaminase, *AST* aspartate transaminase, *LDH* lactate dehydrogenase, *cTnT* cardiac troponin T, *proBNP* pro brain natriuretic peptide

to deliver heated/humidified gas flows, reduce anatomical dead space, and generate low-level PEEP. Nevertheless, there are still some patients whose conditions remain uncontrolled following ventilation, or even experience an exacerbation of their conditions, which increases the risk of death.

The present study sought to examine the characteristics and independent factors predicting treatment failure in patients with acute hypoxaemic expiratory failure treated with high-flow nasal cannula (HFNC). HFNC has been demonstrated to reduce the rate of tracheal intubation in patients with acute hypoxaemic respiratory failure. Our results indicated a failure rate of 34.02% for high-flow oxygenation, a result comparable to that observed in a 2015 multicentre, randomised, open-label trial in which high-flow oxygenation was shown to reduce mortality in the intensive care unit and after 90 days [11]. Two additional studies of novel coronaviruses have demonstrated that HFNC treatment is associated with a reduction in the need for invasive mechanical ventilation compared to COT [12, 13]. The reported failure rates of HFNC treatment in patients with severe COVID-19 infection range from 32 to 57% [14–16]. This may be related to the favourable physiological effects of HFNC [17]. In

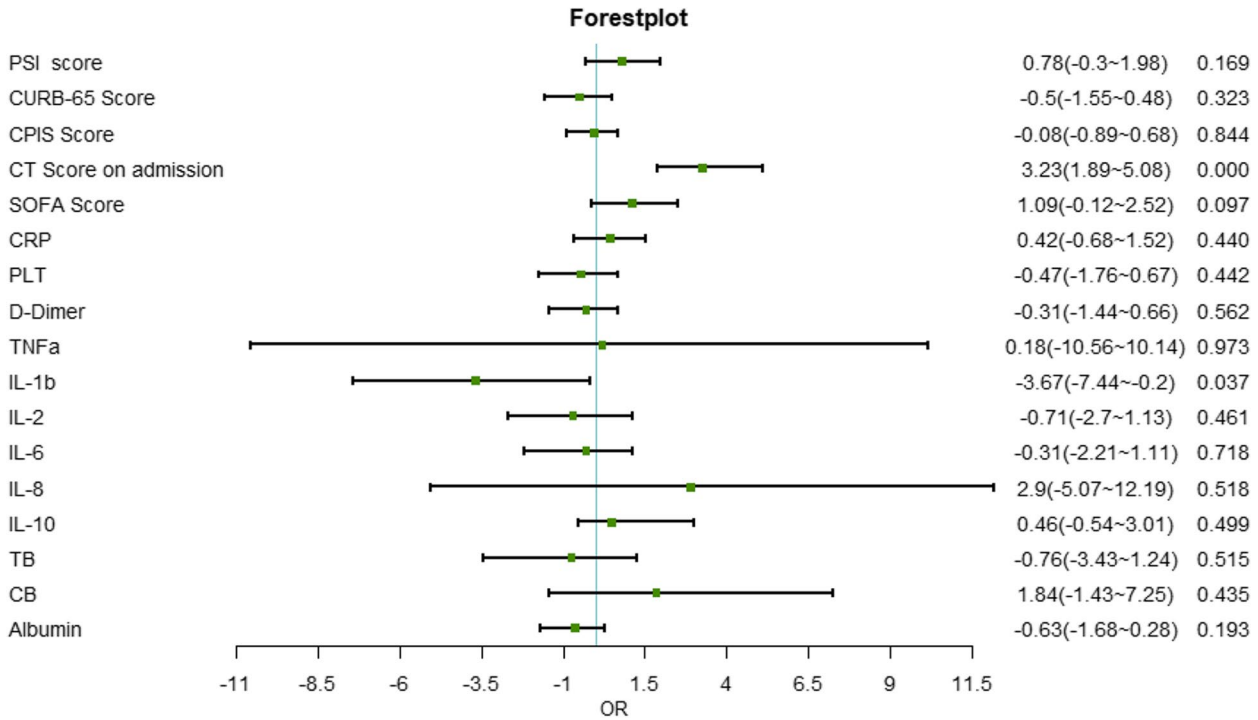

Fig. 2 The multivariate regression analysis for HFNC-F patients

addition, low levels of positive end-expiratory pressure (PEEP) are employed to maintain alveolar patency, nasopharyngeal dead space is flushed to enhance ventilatory efficiency, respiratory patterns are improved, and airway heating and humidification are enhanced. Nevertheless, studies have also reported HFNC failure in 68% of patients. This discrepancy may be attributed to differences in the definition of HFNC failure across studies and the varying severity of disease among the included patients.

Predictors of HFNC failure: Clinical scores and biomarkers. The PSI, CURB-65, CPIS, CT and SOFA scores were found to be significantly higher in the group of patients who did not respond to high-flow oxygen therapy (HFOT) than in those who did respond. In a French study that included 200 patients with COVID-19, the risk factors for HFOT failure were found to be a SAPS-2 score and a CT scan abnormality greater than 75%. These findings are consistent with those of the present study [18].

Physiological and clinical implications. The results demonstrated that HFNC improved oxygenation and respiratory rate. Oxygenation and index (PaO2/FiO2) was significantly lower in the high-flow oxygen therapy failure group than in the success group at 1 h, 6 h, and 12 h of initiating treatment, and respiratory rate was significantly higher in the high-flow oxygen therapy failure group than in the success group. In the HFNC success group, oxygenation and respiratory rate improved after 12 h of treatment. It has been demonstrated that at 4–6 h and 24 h, the respiratory rate decreased in the HFNC group at 4–6 h compared to COT. This is consistent with the results of the present study [13, 19, 20]. A number of studies have demonstrated that HFNC oxygen therapy is more effective than conventional oxygen therapy in improving respiratory rate (RR) and PaO2/FiO2 in patients with acute respiratory failure [17, 21, 22]. The administration of high-flow oxygen through the nasal passages by means of HFNC not only ensures a high oxygen concentration, but also plays an important role in humidifying the airway [23]. A notable enhancement in oxygen saturation was observed following the utilisation of HFNC in patients presenting with acute respiratory failure. This finding aligns with our previous observations and further substantiates the beneficial effects of HFNC in patients requiring respiratory support [5, 24]. A low oxygen saturation on admission is an important predictor of high-flow nasal oxygen failure [25].

The findings underscore the clinical utility of the ROX index (SpO_2/FiO_2 to respiratory rate ratio) in guiding HFNC therapy. HFNC proves effective across diverse populations, including elderly (>75 years) non-COVID ARF patients, improving oxygenation and reducing respiratory distress within 60 min, while maintaining excellent tolerability and safety [26]. In acute hypoxemic

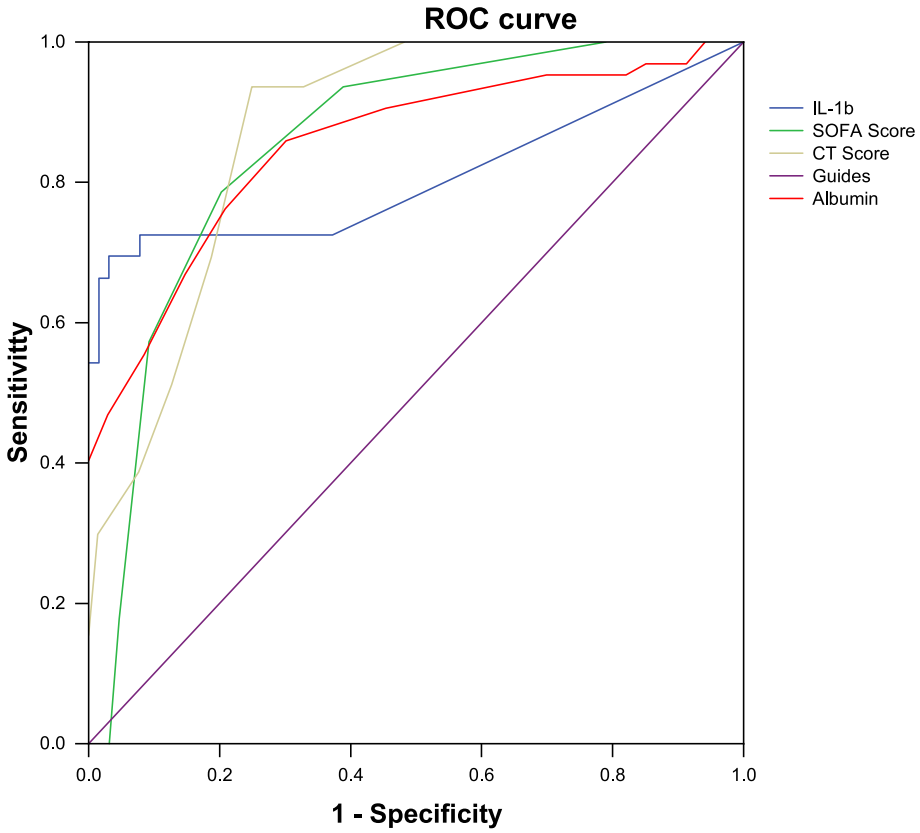

Fig. 3 Receiver operating characteristic (ROC) curve for HFNC-F patients

respiratory failure (AHRF), HFNC reduces intubation needs, though delayed intervention post-failure may increase mortality risk [7]. Notably, HFNC benefits immunocompromised patients by lowering intubation rates, albeit without significant mortality impact, and shows promise in hypercapnic respiratory failure by enhancing comfort and reducing dead space ventilation [27]. Clinicians should tailor ROX thresholds to specific patient groups, monitor HFNC efficacy closely to prevent delayed intubation, and consider HFNC as a safe alternative for patients unsuitable for NIV or ICU admission. These insights reinforce HFNC's role in ARF management while highlighting critical areas for future research.

The levels of CRP, PLT, D-Dimer, TB, CB and IL-10 were found to be significantly higher in the group that had not responded to high flow oxygen therapy, in comparison to the group that had responded. Conversely, the level of albumin was found to be significantly lower in the group that had not responded to high flow oxygen therapy. This reduction in albumin levels has been observed in acutely ill patients [28] and has been associated with a poor prognosis [29]. A study has demonstrated that serum albumin is associated with an increased risk of mortality in patients with COVID-19 [30]. It has been demonstrated that elevated stress CRP, D-dimer, TB and CB levels are associated with increased vascular permeability and organ dysfunction in patients. Furthermore, serum albumin serves as a marker of severe oxidation and is an acute-phase reactant with antioxidant properties. The metabolism of albumin can result in the excretion of reactive oxidants, which can lead to platelet and coagulation activation. This, in turn, can contribute to elevated D-Dimer levels and an increased risk of thrombotic events in critically ill patients with severe hypoalbuminaemia.

In a multivariate logistic regression analysis model, CT score, SOFA score, IL-1β and albumin were identified as independent predictors of treatment failure with high-flow nasal oxygen. In a large study assessing the role of different cytokines in COVID-19 infection, IL-6 demonstrated significant prognostic value [31]. Evaluation of IL-6 levels at the early stage of disease onset allows stratification of higher-risk patients with more severe disease. This study further affirms the value of IL-1β [32].

It should be noted that this study is subject to several limitations. Firstly, this study was retrospective and

conducted in a single centre. Consequently, prospective, multicentre validation studies are required to confirm the findings. Secondly, the study excluded patients with multiple EICU admissions in order to avoid the potential for data duplication and bias. Thirdly, the study excluded children under the age of 14 and elderly patients over the age of 90, as the use of HFNC, which is challenging for patients to cooperate with, may introduce bias into the results. Fourth, as this was a retrospective study, some laboratory data were unavailable or incomplete in the medical records. This limitation may affect the comprehensive analysis of certain clinical parameters, though we mitigated this bias by prioritizing variables with high completeness rates in our inclusion criteria. The results of this study require further validation with a larger sample size from multiple centers.

Conclusion

HFNC is an effective treatment for patients with acute hypoxaemic respiratory failure. The CT score, SOFA score, IL-1β and albumin are independent predictors of failure of high-flow nasal oxygen therapy.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Informed consent

Informed consent was obtained from all the subjects or their legal guardians.

Authors' contributions

Mingming Xue, Fengqing Liao and Feixiang Xu enrolled the patients and designed the study. Mingming Xue, Yumei Chen, Sheng Wang, Yannan Zhou, Hailin Ding and Su Lu contributed to the analysis of the resultes. Mian Shao,Chenling Yao and Zhenju Song designed the study and revised the article.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Fudan University Ethics Committee of Zhongshan Hospital Fudan University (B2023-508R). All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev. 2021;3(3):CD010172.
2. Nishimura M. High-flow nasal cannula oxygen therapy devices. Respir Care. 2019;64(6):735–42.
3. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest. 2015;148(1):253–61.
4. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, Pesenti A. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2017;195(9):1207–15.
5. Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. Respir Care. 2016;61(4):529–41.
6. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernandez G, Garcia-de-Acilu M, Frat JP, Masclans JR, Ricard JD. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019;199(11):1368–76.
7. Ricard JD, Roca O, Lemiale V, Corley A, Braunlich J, Jones P, Kang BJ, Lellouche F, Nava S, Rittayamai N, et al. Use of nasal high flow oxygen during acute respiratory failure. Intensive Care Med. 2020;46(12):2238–47.
8. Carratala JM, Diaz-Lobato S, Brouzet B, Mas-Serrano P, Rocamora JLS, Castro AG, Varela AG, Alises SM. Efficacy and safety of high-flow nasal cannula therapy in elderly patients with acute respiratory failure. Pulmonology. 2024;30(5):437–44.
9. Hernandez G, Dianti J, Paredes I, Moran F, Marquez M, Calle A, Colinas L, Alonso G, Carneiro P, Morales G, et al. Humidified noninvasive ventilation versus high-flow therapy to prevent reintubation in patients with obesity: a randomized clinical trial. Am J Respir Crit Care Med. 2025;211(2):222–9.
10. Investigators R, the BA, Maia IS, Kawano-Dourado L, Tramujas L, de Oliveira NE, Souza RN, Signorini DF, Pincelli MP, Zandonai CL et al: High-Flow Nasal Oxygen vs Noninvasive Ventilation in Patients With Acute Respiratory Failure: The RENOVATE Randomized Clinical Trial. JAMA 2025, 333(10):875–890.
11. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96.
12. Frat JP, Quenot JP, Badie J, Coudroy R, Guitton C, Ehrmann S, Gacouin A, Merdji H, Auchabie J, Daubin C, et al. Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to covid-19: the SOHO-COVID randomized clinical trial. JAMA. 2022;328(12):1212–22.
13. Ospina-Tascon GA, Calderon-Tapia LE, Garcia AF, Zarama V, Gomez-Alvarez F, Alvarez-Saa T, Pardo-Otalvaro S, Bautista-Rincon DF, Vargas MP, Aldana-Diaz JL, et al. Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: a randomized clinical trial. JAMA. 2021;326(21):2161–71.
14. Wang K, Zhao W, Li J, Shu W, Duan J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. Ann Intensive Care. 2020;10(1):37.
15. Vianello A, Arcaro G, Molena B, Turato C, Sukthi A, Guarnieri G, Lugato F, Senna G, Navalesi P. High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection. Thorax. 2020;75(11):998–1000.

16. Covid-Icu group ftRnC-ICUi. Benefits and risks of noninvasive oxygenation strategy in COVID-19: a multicenter, prospective cohort study (COVID-ICU) in 137 hospitals. Crit Care. 2021;25(1):421.
17. Frat JP, Brugiere B, Ragot S, Chatellier D, Veinstein A, Goudet V, Coudroy R, Petitpas F, Robert R, Thille AW, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. Respir Care. 2015;60(2):170–8.
18. AitHamou Z, Levy N, Charpentier J, Mira JP, Jamme M, Jozwiak M. Use of high-flow nasal cannula oxygen and risk factors for high-flow nasal cannula oxygen failure in critically-ill patients with COVID-19. Respir Res. 2022;23(1):329.
19. Sayan I, Altinay M, Cinar AS, Turk HS, Peker N, Sahin K, Coskun N, Demir GD. Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia. Heart Lung. 2021;50(3):425–9.
20. Teng XB, Shen Y, Han MF, Yang G, Zha L, Shi JF. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. Eur J Clin Invest. 2021;51(3):e13435.
21. Schwabbauer N, Berg B, Blumenstock G, Haap M, Hetzel J, Riessen R. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). BMC Anesthesiol. 2014;14:66.
22. Vargas F, Saint-Leger M, Boyer A, Bui NH, Hilbert G. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respir Care. 2015;60(10):1369–76.
23. Li J, Zhao M, Hadeer M, Luo J, Fink JB. Dose response to transnasal pulmonary administration of bronchodilator aerosols via nasal high-flow therapy in adults with stable chronic obstructive pulmonary disease and asthma. Respiration. 2019;98(5):401–9.
24. Grieco DL, Maggiore SM, Roca O, Spinelli E, Patel BK, Thille AW, Barbas CSV, de Acilu MG, Cutuli SL, Bongiovanni F, et al. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. Intensive Care Med. 2021;47(8):851–66.
25. Xia J, Zhang Y, Ni L, Chen L, Zhou C, Gao C, Wu X, Duan J, Xie J, Guo Q, et al. High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: a multicenter, retrospective cohort study. Crit Care Med. 2020;48(11):e1079–86.
26. Diaz-Lobato S, Carratala Perales JM. Efficacy and safety of high-flow nasal cannula therapy in elderly patients with acute respiratory failure. Pulmonology. 2025;31(1):2444727.
27. Vega ML, Pisani L, Dongilli R, Nava S. COVID-19 pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU. Author's reply. Pulmonology. 2022;28(4):322–3.
28. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
29. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, Lin S. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020;92(10):2152–8.
30. Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, Pirro M, Pignatelli P, Lichtner M, Carraro A, et al. Is albumin predictor of mortality in COVID-19? Antioxid Redox Signal. 2021;35(2):139–42.
31. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636–43.
32. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, Klein M, Weinberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-136 e124.

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