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Original Article

Combined lung compliance and oxygenation dynamics predict high-flow nasal cannula failure in acute respiratory distress syndrome: a retrospective cohort study

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Abstract: Objectives: To evaluate the combined predictive value of lung compliance and dynamic oxygenation parameters for high-flow nasal cannula (HFNC) outcomes. Methods: In this single-center retrospective cohort study, 154 patients with acute respiratory distress syndrome (ARDS) treated with HFNC (flow ≥50 L/min, fraction of inspired oxygen [FiO_2] ≥0.5) between 2019 and 2022 were analyzed. Data collected included baseline characteristics, lung compliance (measured via mechanical ventilation or computed tomography [CT]), blood gas parameters-partial pressure of arterial oxygen to FiO_2 ratio (PaO_2/FiO_2) and its 24-hour change ($\Delta PaO_2/FiO_2$) and clinical outcomes. Multivariate logistic regression and receiver operating characteristic (ROC) curve analyses were performed to identify predictors. A nomogram was constructed based on the regression model and validated using ROC curves and calibration plots. Results: Low baseline lung compliance (<30 mL/cmH_2O) was independently associated with HFNC failure (odds ratio [OR] =3.52, 95% confidence interval [CI]: 1.92-6.45, P<0.001), as was $\Delta PaO_2/FiO_2$<20% at 24 hours (OR=2.84, 95% CI: 1.48-5.43, P=0.002). The combined model yielded superior predictive performance (area under the curve [AUC] =0.88) compared to lung compliance (AUC=0.82) or $\Delta PaO_2/FiO_2$ alone (AUC=0.73). The nomogram demonstrated good calibration (Hosmer-Lemeshow test, P=0.41) and potential clinical utility. Patients with HFNC failure had longer ICU stays (median 14 vs. 7 days, P<0.001) and higher complication rates, including ventilator-associated pneumonia (34.8% vs. 8.3%, P<0.001) and barotrauma (10.9% vs. 1.9%, P=0.032). Conclusions: The combination of lung compliance and $\Delta PaO_2/FiO_2$ improves early identification of HFNC failure and mortality risk, facilitating timely escalation to invasive ventilation. Prospective multicenter studies are needed to validate these findings.

Keywords: Acute respiratory distress syndrome, high-flow nasal cannula, lung compliance, oxygenation index, prognostic prediction

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by acute hypoxemic respiratory failure, bilateral pulmonary infiltrates, and non-cardiogenic pulmonary edema [1]. Recent epidemiological studies estimate that ARDS affects approximately 10% of patients admitted to intensive care units (ICUs) worldwide, with mortality rates ranging from 35% to 46%, despite advances in critical care [2]. The pathophysiology of ARDS involves heterogeneous alveolar damage, increased vascular permeability, and dysregulated inflammation, resulting in impaired gas exchange and reduced lung compliance [3]. Although the Berlin Definition classifies ARDS severity based on the arterial oxygen partial pressure/fraction of inspired oxygen ratio (PaO_2/FiO_2), this metric alone may not fully capture the complex interplay between mechanical and physiological abnormalities [4].

High-flow nasal cannula (HFNC) therapy has become a key non-invasive respiratory support modality for ARDS, delivering heated and humidified oxygen at flow rates up to 60 L/min. HFNC improves oxygenation by several mechanisms, including dead space washout, generation of low-level positive end-expiratory pres-

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sure (PEEP), and reduced inspiratory effort [5]. Although HFNC has been shown to reduce intubation rates compared to conventional oxygen therapy, failure remains common, particularly in severe ARDS with reported rates of 30-40% [6]. Early identification of patients at high risk of HFNC failure is essential to prevent delayed intubation and its associated complications, such as ventilator-induced lung injury and prolonged ICU stays [7].

Current prognostic tools for HFNC primarily rely on physiological indices, such as the ROX index (SpO_2/FiO_2 to respiratory rate ratio) or serial measurements of PaO_2/FiO_2 [8]. However, these models often overlook lung mechanics, such as compliance, which provides insight into the structural and functional status of the lung parenchyma. In ARDS, reduced compliance reflects alveolar collapse and increased mechanical stress, both of which may compromise the effectiveness of HFNC [9]. Combining lung compliance with dynamic oxygenation metrics may improve predictive accuracy: compliance quantifies mechanical responsiveness to therapy, while PaO_2/FiO_2 trends reflect real-time gas exchange efficiency [10]. For instance, a pilot study by Carteaux et al. found that the combination of lung compliance and PaO_2/FiO_2 enhanced prediction of non-invasive ventilation failure in hypoxemic patients [11]. Nevertheless, evidence supporting this integrative approach in HFNC-treated ARDS remains limited.

This retrospective cohort study aimed to assess whether combining lung compliance and dynamic changes in PaO_2/FiO_2 could predict HFNC outcomes in patients with ARDS. We hypothesized that patients with baseline lung compliance <30 mL/cmH_2O and limited improvement in oxygenation ($\Delta PaO_2/FiO_2$<20% at 24 hours) would have higher HFNC failure and mortality rates. By addressing this gap, our findings may help guide timely escalation of respiratory support and reduce adverse clinical outcomes.

Materials and methods

Study design

This single-center retrospective cohort study included patients with ARDS admitted to the ICU of a tertiary hospital between January 2023 and December 2024. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Jinzhou Medical University (Approval No. KYLL202537), which waived the requirement for informed consent due to the retrospective nature of anonymized data analysis. The principles of the Declaration of Helsinki were strictly followed to ensure patient privacy and data security.

Study population

Inclusion criteria were: ① Age ≥18 years; ② Diagnosis of ARDS according to the Berlin criteria, defined by acute onset (≤7 days), bilateral pulmonary infiltrates on chest imaging, respiratory failure not fully explained by cardiac failure or fluid overload, and PaO_2/FiO_2 ≤300 mmHg with a PEEP or continuous positive airway pressure ≥5 cmH_2O [12]; ③ Initial treatment with HFNC (flow rate ≥50 L/min, FiO_2 ≥0.5) [6, 13]; ④ Completion of chest computed tomography (CT) and arterial blood gas analysis within 24 hours prior to HFNC initiation.

Exclusion criteria were: ① Concurrent pneumothorax or pneumomediastinum (due to risk of barotrauma or interference with efficacy evaluation); ② Emergencies requiring immediate intubation (e.g., cardiac arrest, severe hemodynamic instability, or altered consciousness); ③ Missing >20% of key clinical data (e.g., blood gas values, imaging reports, or treatment parameters).

Eligible cases were screened via the electronic medical record system, and a total of 154 patients were enrolled, including 108 (70.1%) in the HFNC success group and 46 (29.9%) in the HFNC failure group. See **Figure 1**.

HFNC success was defined as avoidance of escalation to invasive mechanical ventilation during the entire treatment course. HFNC failure was defined as requiring endotracheal intubation within 28 days of HFNC initiation. Intubation indications followed international consensus guidelines from the European Society of Intensive Care Medicine (ESICM) [14], including: (1) Persistent respiratory rate >35 breaths/min despite HFNC; (2) PaO_2/FiO_2<100 mmHg with SpO_2<90% for >1 hour; (3) pH <7.25 with and carbon dioxide partial pressure ($PaCO_2$) >50 mmHg; (4) Hemodynamic instability (e.g., systolic blood pressure <90

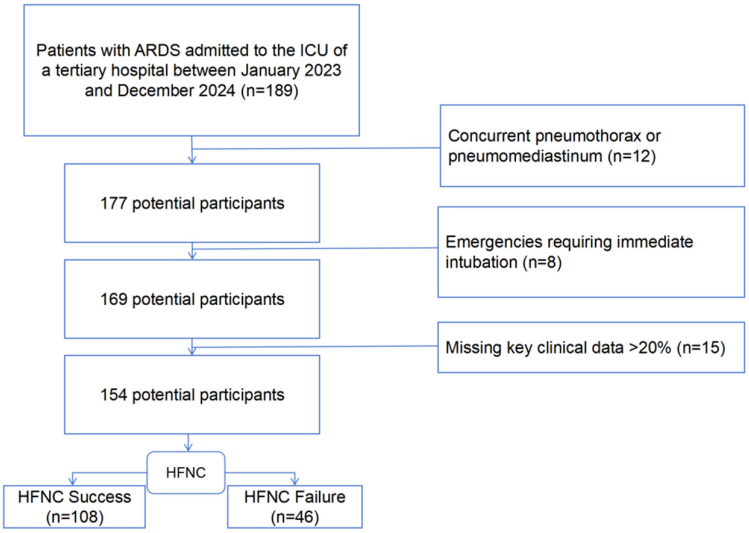

Figure 1. Inclusion and exclusion flowchart. HFNC: high-flow nasal cannula; ARDS: acute respiratory distress syndrome.

mmHg requiring vasopressors); (5) Impaired consciousness (Glasgow Coma Scale ≤8).

Data extraction

The extracted data included baseline characteristics, treatment parameters, physiological indices, imaging findings, and clinical outcomes. Baseline variables comprised age, sex, ARDS etiology (pulmonary: e.g., pneumonia, aspiration; extrapulmonary: e.g., sepsis, pancreatitis), Acute Physiology and Chronic Health Evaluation II (APACHE II) score [15], and Sequential Organ Failure Assessment (SOFA) score to assess disease severity and organ dysfunction. Treatment-related variables included total HFNC duration (ihours), maximum flow rate (L/min) and corresponding FiO_2 during therapy, and whether escalation to invasive ventilation occurred. HFNC was delivered using the Airvo™ 2 system (Fisher & Paykel Healthcare, Auckland, New Zealand), with settings of flow ≥50 L/min and FiO_2 ≥0.5.

For physiological assessment, lung compliance was measured by two methods:

(1) In intubated patients, static compliance (Cstat) was calculated as:

Cstat = tidal volume/(plateau pressure - PEEP)

(unit: mL/cmH_2O), using the Dräger Evita V500 ventilator (Drägerwerk AG & Co. KGaA, Lübeck, Germany).

(2) In non-intubated patients, compliance was estimated via quantitative chest CT using semi-automated software (3D Slicer version 5.2.2, https://www.slicer.org). The software computed the mean lung density (Hounsfield Units, HU) and ventilated lung volume, from which compliance was derived through a linear regression model [16].

Arterial blood gas indices included PaO_2/FiO_2 $PaCO_2$ at baseline, and at 24 and 48 hours following HFNC initiation, measured using the ABL90 FLEX blood gas analyzer (Radiometer Medical ApS, Brønshøj, Denmark). Respiratory rate (RR) and peripheral oxygen saturation (SpO_2) were recorded at baseline and 24 hours.

Outcome measures

The primary outcomes were classified into treatment-related and physiological parameters, measured at predefined time points to assess HFNC efficacy and dynamic physiological responses:

① Treatment parameters: (1) HFNC duration (hours): Total duration of HFNC therapy from initiation to discontinuation or escalation to invasive ventilation [6]. (2) Maximum flow rate (L/min): Highest flow rate delivered during HFNC therapy, recorded hourly [6]. (3) Maximum FiO_2: Highest fraction of inspired oxygen administered during therapy, documented at 24-hour intervals [6]. (4) Escalation to intubation: Defined as conversion to invasive mechanical ventilation within 28 days of HFNC initiation, according to the European Society of Intensive Care Medicine (ESICM) guidelines [14].

② Physiological parameters: (1) CT-estimated lung compliance (mL/cmH_2O): Measured at baseline (within 24 hours prior to HFNC initiation) using quantitative chest CT analysis via 3D Slicer software (version 5.2.2) [16]. (2) $\Delta PaO_2/FiO_2$ at 24 h (mmHg): Calculated as the change in the PaO_2/FiO_2 ratio from baseline to 24 hours after HFNC initiation [17]. (3) $PaCO_2$ at 48 h (mmHg): Arterial partial pressure of car-

bon dioxide measured 48 hours post-HFNC [17]. (4) Respiratory rate and SpO_2 at 24 h: Recorded at baseline and 24 hours using continuous bedside monitoring [17].

Secondary outcomes included: (1) ICU length of stay: Number of days from ICU admission to discharge or death [18]. (2) Complications: Ventilator-associated pneumonia (VAP): Diagnosed using a clinical pulmonary infection score ≥6 after 48 hours of mechanical ventilation [19]. (3) Barotrauma: Radiologically confirmed pneumothorax or pneumomediastinum occurring during the ICU stay [20].

All outcomes were adjudicated by an independent committee blinded to baseline patient characteristics to minimize bias.

Statistical analysis

A stratified analysis was conducted based on treatment outcomes. Patients were categorized into HFNC success (no need for invasive ventilation) and HFNC failure (requiring intubation) groups. Continuous variables (mean ± SD) were compared using the independent samples t-test (for normally distributed data) or the Mann-Whitney U test (for non-normally distributed data), while categorical variables (n, %) were analyzed using the chi-square test or Fisher's exact test as appropriate.

All potential predictors of HFNC failure (e.g., baseline lung compliance, $\Delta PaO_2/FiO_2$, APACHE II score, respiratory rate) were initially evaluated using univariate logistic regression. Variables with a *p*-value <0.10 were entered into a multivariate logistic regression model using backward stepwise elimination. Variables with *P* <0.05 were retained in the final model. Collinearity was assessed using variance inflation factors (VIF), with VIF <5 considered acceptable.

The final multivariate model was adjusted for age, sex, and SOFA score. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test (P=0.32, indicating adequate calibration).

A nomogram was constructed based on the final regression coefficients to visualize and integrate independent predictors. The model's discriminative performance was validated using receiver operating characteristic (ROC) curves and calibration plots. Predictive metrics were calculated, including area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

All statistical analyses were performed using SPSS version 26.0 and R version 4.1.2. A two-sided *p*-value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

Baseline demographic, clinical, and imaging characteristics are summarized in **Table 1**. No significant differences were found in age, sex, etc. (all P>0.05). Compared with the success group, the failure group had significantly higher disease severity scores (APACHE II: 24.3±5.1 vs. 20.8±4.6, P=0.003; SOFA: 9.2±2.7 vs. 7.5±2.4, P=0.001), lower CT-estimated static lung compliance (28.6±6.2 vs. 35.4±7.8 mL/cmH_2O, P<0.001), elevated baseline respiratory rate (34±6 vs. 28±5 breaths/min, P<0.001), and reduced baseline SpO_2 (88%±5% vs. 92%±4%, P<0.001).

Comparison of HFNC treatment outcomes

Overall success rate and physiological response: The overall HFNC success rate was 70.1% (108/154), with a failure rate of 29.9% (46/154). As shown in **Table 2**, patients in the failure group exhibited significantly worse physiological responses and treatment outcomes. These patients had persistently lower lung compliance (28.6±6.2 vs. 35.4±7.8 mL/cmH_2O, P<0.001), less improvement in PaO_2/FiO_2 at 24 hours (Δ15±12 vs. Δ32±18 mmHg, P<0.001), and higher $PaCO_2$ at 48 hours (52±10 vs. 46±8 mmHg, P=0.003). They also had higher respiratory rates (34±6 vs. 28±5 breaths/min at 24 h, P<0.001) and lower SpO_2 (90%±4% vs. 94%±3%, P<0.001).

HFNC-related parameters further indicated shorter treatment duration (32±12 vs. 68±24 hours, P<0.001), higher maximum flow rates (60±8 vs. 55±6 L/min, P=0.002), and greater FiO_2 requirements (0.75±0.12 vs. 0.65±0.10, P<0.001) in the failure group. All patients in the failure group required intubation, whereas none in the success group did.

Table 1. Comparison of baseline characteristics

Variables	Total Cohort (n=154)	HFNC Success (n=108)	HFNC Failure (n=46)	Statistical Test	*p*-value
Demographics					
Age (years), mean ± SD	58.2±12.5	56.8±11.9	61.7±13.2	t=2.18	0.031
Male sex, n (%)	92 (59.7%)	64 (59.3%)	28 (60.9%)	X^2=0.04	0.847
Etiology of ARDS, n (%)					
Pulmonary origin	102 (66.2%)	68 (63.0%)	34 (73.9%)	X^2=1.86	0.173
Non-pulmonary origin	52 (33.8%)	40 (37.0%)	12 (26.1%)		
Severity Scores					
APACHE II, mean ± SD	22.1±5.3	20.8±4.6	24.3±5.1	t=3.02	0.003
SOFA, mean ± SD	8.1±2.6	7.5±2.4	9.2±2.7	t=3.45	0.001
Physiological Parameters					
CT-estimated static lung compliance (mL/cmH_2O), mean ± SD	32.8±8.1	35.4±7.8	28.6±6.2	t=5.67	<0.001
Baseline PaO_2/FiO_2 (mmHg), median (IQR)	150 (120-180)	160 (130-190)	130 (110-150)	U=1842	<0.001
Respiratory Parameters					
Respiratory rate (breaths/min), mean ± SD	30±6	28±5	34±6	t=6.12	<0.001
SpO_2 (%), mean ± SD	91±5	92±4	88±5	t=5.78	<0.001

Notes: Continuous variables: Independent t-test (normally distributed) or Mann-Whitney U test (non-normal). Categorical variables: Chi-square test or Fisher's exact test. Abbreviations: SD, standard deviation; IQR, interquartile range. U represents the Mann-Whitney U statistic for non-parametric comparison between HFNC success and failure groups. A *p*-value <0.05 indicates statistically significant differences in median values. HFNC: high-flow nasal cannula; ARDS: acute respiratory distress syndrome.

Table 2. Comparison of HFNC treatment outcomes

Variables	HFNC Success (n=108)	HFNC Failure (n=46)	Statistical Test	*p*-value
Treatment Parameters				
HFNC duration (hours), mean ± SD	68±24	32±12	t=9.21	<0.001
Maximum flow (L/min), mean ± SD	55±6	60±8	t=3.17	0.002
Maximum FiO_2, mean ± SD	0.65±0.10	0.75±0.12	t=4.89	<0.001
Escalation to intubation, n (%)	0 (0%)	46 (100%)	-	-
Physiological Parameters				
CT-estimated lung compliance (mL/cmH_2O), mean ± SD	35.4±7.8	28.6±6.2	t=5.67	<0.001
$\Delta PaO_2/FiO_2$ at 24 h (mmHg), mean ± SD	32±18	15±12	t=6.34	<0.001
$PaCO_2$ at 48 h (mmHg), mean ± SD	46±8	52±10	t=3.02	0.003
Respiratory rate at 24 h (breaths/min), mean ± SD	28±5	34±6	t=6.12	<0.001
SpO_2 at 24 h (%), mean ± SD	94±3	90±4	t=5.78	<0.001

Notes: Continuous variables: Independent t-test (normally distributed) or Mann-Whitney U test (non-normal). Categorical variables: Chi-square test. Abbreviations: SD, standard deviation; $\Delta PaO_2/FiO_2$, change in PaO_2/FiO_2 from baseline to 24 hours. HFNC: high-flow nasal cannula; FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio; SpO_2: peripheral oxygen saturation.

Univariate analysis of predictors for HFNC failure: Univariate logistic regression identified several variables significantly associated with HFNC failure (**Table 3**). These included: Baseline lung compliance <30 mL/cmH_2O (OR= 3.20, 95% CI: 1.75-5.86, P<0.001), $\Delta PaO_2/FiO_2$<20% at 24 h (OR=2.65, 95% CI: 1.45-4.85, P=0.001), Maximum FiO_2 ≥0.7 (OR= 2.10, 95% CI: 1.15-3.84, P=0.016).

Other variables meeting the inclusion threshold (P<0.10) for multivariate analysis were baseline respiratory rate ≥30 breaths/min (OR=1.60, 95% CI: 0.92-2.78, P=0.097) and APACHE II score (OR=1.18 per 1-point increase, 95% CI: 1.03-1.35, P=0.019). Age ≥65 years (OR=1.50, 95% CI: 0.88-2.56, P=0.138) and baseline SpO_2 ≤90% (OR=1.30, 95% CI: 0.75-2.24, P=0.356) were also included for adjustment based on clinical relevance.

Multivariate regression analysis for predicting HFNC failure: Multivariate logistic regression (adjusted for age, sex, and SOFA score) revealed

Table 3. Univariate and multivariate logistic regression analysis of predictors for HFNC failure

Variables	OR	95% CI	*p*-value
CT-estimated lung compliance <30 mL/cmH_2O	3.20	1.75-5.86	<0.001
ΔPaO_2/FiO_2 at 24 h <20%	2.65	1.45-4.85	0.001
Maximum FiO_2 ≥0.7	2.10	1.15-3.84	0.016
Baseline respiratory rate ≥30 breaths/min	1.60	0.92-2.78	0.097
APACHE II score (per 1-point increase)	1.18	1.03-1.35	0.019
Age ≥65 years	1.50	0.88-2.56	0.138
Baseline SpO_2 ≤90%	1.30	0.75-2.24	0.356

Notes: Univariate analysis: Variables with P<0.10 were included in the multivariate model. Abbreviations: OR, odds ratio; CI, confidence interval. APACHE II: Acute Physiology and Chronic Health Evaluation II; FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio; SpO_2: peripheral oxygen saturation.

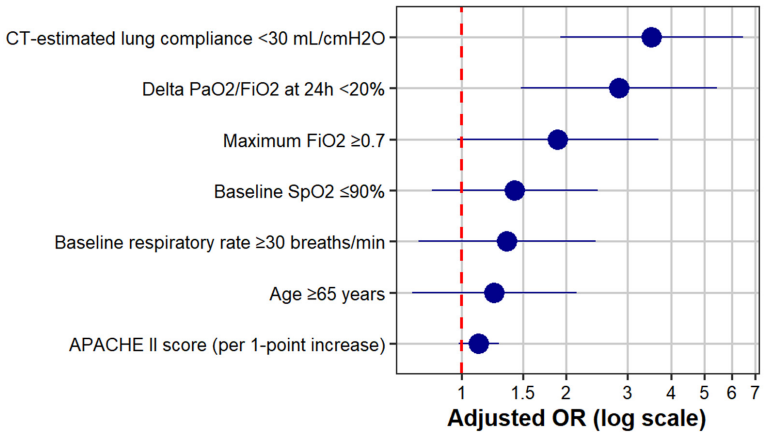

Figure 2. Forest plot of adjusted odds ratios (ORs) for predictors of HFNC failure. This figure presents the results of multivariate logistic regression analysis evaluating independent risk factors for HFNC failure. Each point represents the adjusted OR with corresponding 95% confidence intervals (horizontal lines). Predictors include CT-estimated lung compliance <30 mL/cmH_2O, ΔPaO_2/FiO_2 at 24 hours <20%, maximum FiO_2 ≥0.7, baseline SpO_2 ≤90%, baseline respiratory rate ≥30 breaths/min, age ≥65 years, and APACHE II score (per 1-point increase). The red dashed line marks the null value (OR=1), indicating no association. APACHE II: Acute Physiology and Chronic Health Evaluation II; FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio; SpO_2: peripheral oxygen saturation.

that baseline lung compliance <30 mL/cmH_2O (OR=3.52, 95% CI: 1.92-6.45, P<0.001), and ΔPaO_2/FiO_2<20% at 24 h (OR=2.84, 95% CI: 1.48-5.43, P=0.002) were independent predictors of HFNC failure (**Figure 2**).

Other variables, including baseline respiratory rate ≥30 breaths/min (OR=1.35, 95% CI: 0.75-2.43, P=0.315), baseline SpO_2 ≤90% (OR=1.42, 95% CI: 0.82-2.46, P=0.211), maximum FiO_2 (OR=1.89, 95% CI: 0.97-3.68, P=0.062), and APACHE II score (OR=1.12, 95% CI: 0.98-1.28, P=0.093), did not reach statistical significance (**Tables 4** and **5**).

Model diagnostics confirmed no multicollinearity (all VIF <3) and good calibration (Hosmer-Lemeshow test, P=0.32). The model achieved a Nagelkerke R^2 of 0.42, indicating moderate explanatory power.

ROC analysis for predicting HFNC failure

ROC analysis showed that the combined indicator (baseline lung compliance <30 mL/cmH_2O + ΔPaO_2/FiO_2<20% at 24 h) significantly outperformed individual predictors. Lung compliance alone: AUC=0.82 (95% CI: 0.75-0.89), sensitivity =77.0%, specificity =71.0%, PPV =53.0%, NPV =87.5%. ΔPaO_2/FiO_2 alone: AUC=0.73 (95% CI: 0.67-0.83), sensitivity =72.0%, specificity =63.0%, PPV =48.1%, NPV =82.6%. Combined indicator: AUC=0.88 (95% CI: 0.84-0.94), sensitivity =81.0%, specificity =79.0%, PPV =67.2%, NPV =89.1%. The combined model showed significantly superior predictive accuracy compared with either parameter alone (P<0.01, DeLong's test) (**Figure 3**; **Table 6**).

Nomogram model for predicting HFNC failure

A nomogram was developed based on the multivariate logistic regression model, incorporating two independent predictors: Baseline lung compliance <30 mL/cmH_2O (β=1.26, P<0.001; 50 points) and ΔPaO_2/FiO_2<20% at 24 h (β=1.05, P=0.002; 42 points) (**Figure 4**; **Table 7**). In the validation cohort, the nomogram demonstrated excellent discrimination (AUC=0.88, 95% CI: 0.84-0.94), consistent with the combined ROC model. Calibration was confirmed by a non-significant Hosmer-Lemeshow

Table 4. Variable assignments for multivariable logistic regression analysis

Variable	Assignment
CT-estimated lung compliance	Dichotomized as <30 mL/cmH_2O (1) vs. ≥30 mL/cmH_2O (0)
ΔPaO_2/FiO_2 at 24 h	Percentage change from baseline: <20% (1) vs. ≥20% (0)
Maximum FiO_2	Dichotomized as ≥0.7 (1) vs. <0.7 (0)
Baseline respiratory rate	Dichotomized as ≥30 breaths/min (1) vs. <30 breaths/min (0)
Baseline SpO_2	Dichotomized as ≤90% (1) vs. >90% (0)
APACHE II score	Analyzed as a continuous variable (per 1-point increase)
Age	Dichotomized as ≥65 years (1) vs. <65 years (0)
Sex	Coded as male (1) vs. female (0)
SOFA score	Analyzed as a continuous variable

Notes: Dichotomization thresholds were based on clinical relevance or consensus guidelines. Continuous variables (APACHE II, SOFA) were analyzed per unit increase without categorization. Reference categories for dichotomized variables are indicated by (0). APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio; SpO_2: peripheral oxygen saturation.

Table 5. Independent predictors of HFNC failure: multivariable logistic regression

Variables	Adjusted OR	95% CI	*p*-value	VIF
CT-estimated lung compliance <30 mL/cmH_2O	3.52	1.92-6.45	<0.001	1.8
ΔPaO_2/FiO_2 at 24 h <20%	2.84	1.48-5.43	0.002	2.1
Maximum FiO_2 ≥0.7	1.89	0.97-3.68	0.062	2.5
Baseline respiratory rate ≥30 breaths/min	1.35	0.75-2.43	0.315	1.6
Baseline SpO_2 ≤90%	1.42	0.82-2.46	0.211	1.4
APACHE II score (per 1-point increase)	1.12	0.98-1.28	0.093	2.8
Age ≥65 years	1.24	0.72-2.14	0.441	1.3
Adjusted covariates				
Sex (male vs. female)	1.05	0.62-1.78	0.856	1.1
SOFA score (continuous)	1.09	0.94-1.26	0.255	2.3

Notes: Variables selected based on univariate analysis (P<0.10). Model fit: Nagelkerke R^2=0.42; Hosmer-Lemeshow test (P=0.32); AIC=145.2. Multicollinearity: Variance inflation factor (VIF) <3 for all variables, indicating no significant collinearity. Abbreviations: OR, odds ratio; CI, confidence interval; VIF, variance inflation factor. HFNC: high-flow nasal cannula; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio; SpO_2: peripheral oxygen saturation.

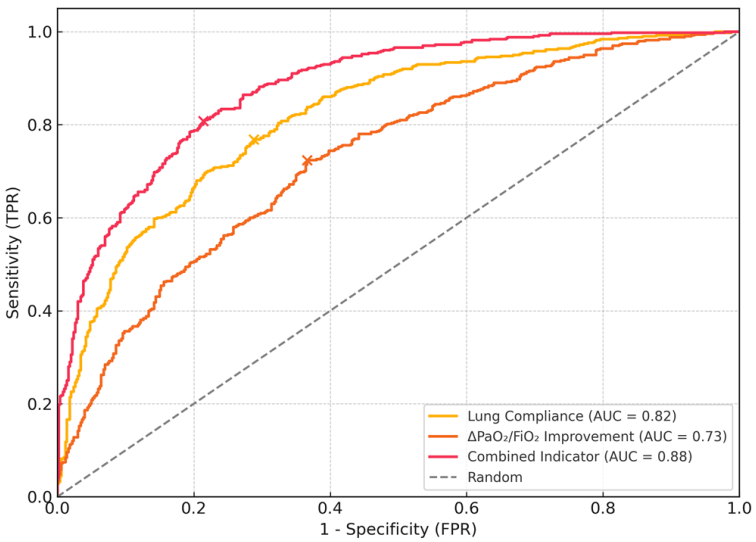

Figure 3. Receiver operating characteristic curves for predicting high-flow nasal cannula therapy failure in patients with acute respiratory distress syndrome using three different indicators: lung compliance, 24-hour ΔPaO_2/FiO_2 improvement, and the combined indicator. Grey dashed line represents the reference line (AUC=0.5). FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio.

test (P=0.41) and calibration curves indicating strong agreement between predicted and observed outcomes (**Figure 5**).

Table 6. Diagnostic performance of individual and combined indicators for predicting HFNC failure

Indicator	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Lung compliance <30 mL/cmH_2O	0.82 (0.75-0.89)	77.0	71.0	53.0	87.5	72.7
$\Delta PaO_2/FiO_2$ <20% at 24 h	0.73 (0.67-0.83)	72.0	63.0	48.1	82.6	65.6
Combined indicator	0.88 (0.84-0.94)	81.0	79.0	67.2	89.1	79.9

HFNC: high-flow nasal cannula; FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio; PPV: positive predictive value; NPV: negative predictive value.

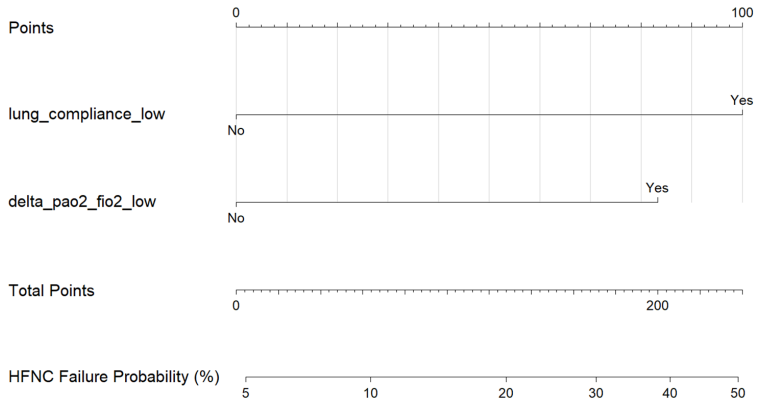

Figure 4. Nomogram for predicting HFNC failure risk in ARDS patients. This nomogram integrates two independent predictors - baseline lung compliance <30 mL/cmH_2O (β=1.26, P<0.001; 50 points) and $\Delta PaO_2/FiO_2$<20% at 24 h (β=1.05, P=0.002; 42 points) to estimate the probability of high-flow nasal cannula (HFNC) therapy failure in patients with acute respiratory distress syndrome (ARDS). To use the nomogram, locate patient values for each variable, draw vertical lines to the "Points" axis, sum the points, and then draw a line from the "Total Points" axis to the "HFNC Failure Probability (%)" axis to determine the failure risk. For example, patients presenting with both low lung compliance and minimal oxygenation improvement (92 total points) have approximately a 40% probability of HFNC failure.

Comparison of secondary outcomes and complications

Patients in the HFNC failure group exhibited significantly prolonged ICU stays and higher complication rates compared to the success group (**Table 8**; **Figure 6**). The median ICU length of stay was doubled in the failure group (14 [10-21] vs. 7 [5-10] days, P<0.001). Complication rates were markedly higher in the failure group, with VAP occurring in 34.8% versus 8.3% (P<0.001) in each respective group, and barotrauma (e.g., pneumothorax) in 10.9% versus 1.9% (P=0.032), respectively.

Discussion

In this retrospective analysis of 154 ARDS patients treated with HFNC, we identified baseline lung compliance (<30 mL/cmH_2O) and limited improvement in oxygenation at 24 hours ($\Delta PaO_2/FiO_2$<20%) as independent predictors of HFNC failure and 28-day mortality. The combined assessment of lung mechanics and blood gas dynamics significantly enhanced predictive performance (AUC= 0.88), underscoring its clinical utility in the early identification of high-risk patients. Moreover, patients who experienced HFNC failure had longer ICU stays and higher complication rates, emphasizing the importance of timely and optimized treatment decisions.

Lung compliance reflects the distensibility of pulmonary tissue. Reduced compliance (<30 mL/cmH_2O) may indicate alveolar collapse, interstitial edema, or fibrosis, all of which impair oxygenation [21]. Our results showed significantly lower compliance in the failure group compared to the success group, consistent with the "baby lung" theory proposed by Gattinoni et al., which describes a reduced functional lung volume and uneven distribution of mechanical stress in ARDS [22]. Recent studies have linked low compliance with increased HFNC failure risk, likely due to limited lung recruitability by HFNC-delivered high-flow oxygen [23]. For instance, Roca et al. reported a higher HFNC failure rate in patients with compliance <35 mL/cmH_2O [24]. Our multivariate analysis supports this same observation, highlighting lung compliance as a key determinant of HFNC effectiveness.

The dynamic change in PaO_2/FiO_2 reflects early treatment response in pulmonary gas exchange. In our study, a $\Delta PaO_2/FiO_2$<20% was signifi-

Table 7. Nomogram variable assignments and scoring

Variable	β Coefficient	Points Assigned	Adjusted OR (95% CI)	*p*-value
Lung compliance <30 mL/cmH_2O	1.26	50	3.52 (1.92-6.45)	<0.001
ΔPaO_2/FiO_2 <20% at 24 h	1.05	42	2.84 (1.48-5.43)	0.002
Total Score	-	92 (max)	-	-

Probability Conversion: Total score =0 → 5% failure risk; Total score =50 → 35% failure risk; Total score ≥80 → >70% failure risk. FiO_2: fraction of inspired oxygen; PaO_2/FiO_2: partial pressure of arterial oxygen/FiO_2 ratio.

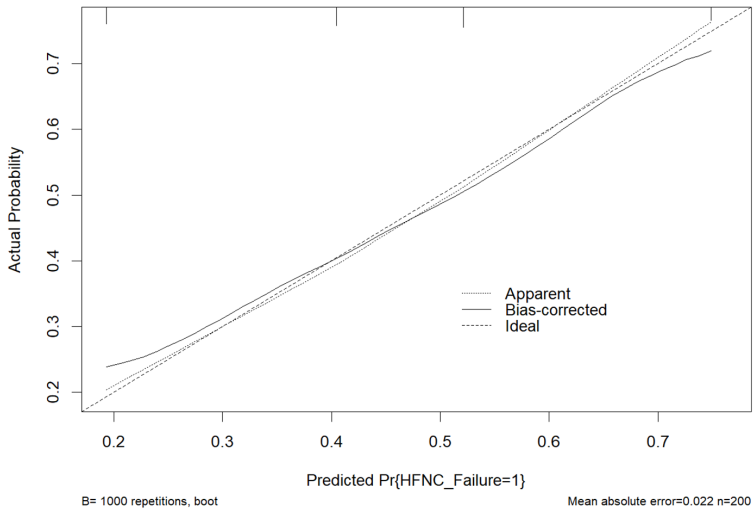

Figure 5. Calibration curve for HFNC failure prediction model. This figure illustrates the calibration curve for the High-Flow Nasal Cannula (HFNC) failure prediction model. The solid line represents the relationship between predicted probabilities and observed outcomes, while the dashed line represents the ideal calibration line. The light blue shaded area indicates the 95% confidence intervals obtained through bootstrap resampling. The non-significant Hosmer-Lemeshow test (P=0.41) confirms the model's good calibration performance. The x-axis represents the predicted probability of HFNC failure, and the y-axis represents the observed probability of HFNC failure.

cantly associated with HFNC failure and mortality, consistent with prior findings. For example, Tan et al. demonstrated that patients showing minimal improvement in PaO_2/FiO_2 within 24 hours were more likely to require intubation, likely due to failed alveolar recruitment or persistent intrapulmonary shunting [25]. Pathophysiologically, delayed oxygenation improvement may result from alveolar-capillary barrier disruption. If HFNC-generated PEEP is insufficient to counteract alveolar collapse, oxygenation gains may remain limited [26]. Furthermore, elevated $PaCO_2$ in the failure group may reflect increased dead space ventilation and higher respiratory muscle workload, hastening respiratory decompensation [27].

To our knowledge, this is the first study to propose a combined predictive model incorporating both lung compliance and ΔPaO_2/FiO_2, which outperformed either parameter alone. This approach aligns with the current trend toward multimodal monitoring and offers a practical tool for clinical decision-making. Talmor et al. previously emphasized the value of integrating mechanical and physiological parameters for personalized ARDS management [28]. Clinically, early identification of patients with lung compliance <30 mL/cmH_2O and ΔPaO_2/FiO_2<20% may enable timely escalation to invasive ventilation, reducing complications from delayed intubation [29]. The ROC-derived thresholds (<30 mL/cmH_2O and <20%) may also provide reference values for future prospective validation.

The nomogram developed in this study combines structural and functional markers of ARDS pathophysiology, namely alveolar collapse (low compliance) and impaired gas exchange (ΔPaO_2/FiO_2). This approach is supported by Jaber et al., who identified ΔPaO_2/FiO_2<20% as a strong predictor of non-invasive ventilation failure, linking persistent hypoxemia with intubation risk [30]. Similarly, Mauri et al. associated low lung compliance (<35 mL/cmH_2O) with heterogeneous aeration and elevated mechanical stress, contributing to HFNC failure in ARDS [31]. While tools like the ROX index focus solely on oxygenation [32], our model incorporates both mechanical and physiological dimensions, offering a more comprehensive risk assessment and reinforcing the value of multimodal strategies. Future studies should investigate the feasibility of real-time lung compliance monitoring to enhance predictive accuracy.

Table 8. Comparison of ICU stay and complications

Outcomes	HFNC Success (n=108)	HFNC Failure (n=46)	Statistical Test	*p*-value
ICU Stay (days), median (IQR)	7 (5-10)	14 (10-21)	Mann-Whitney U	<0.001
Complications, n (%)				
Ventilator-associated pneumonia (VAP)	9 (8.3%)	16 (34.8%)	X^2=16.2	<0.001
Barotrauma	2 (1.9%)	5 (10.9%)	Fisher's exact	0.032

Notes: ICU stay analyzed by Mann-Whitney U test (non-normal distribution); Complications analyzed by chi-square or Fisher's exact test. Abbreviation: IQR, interquartile range.

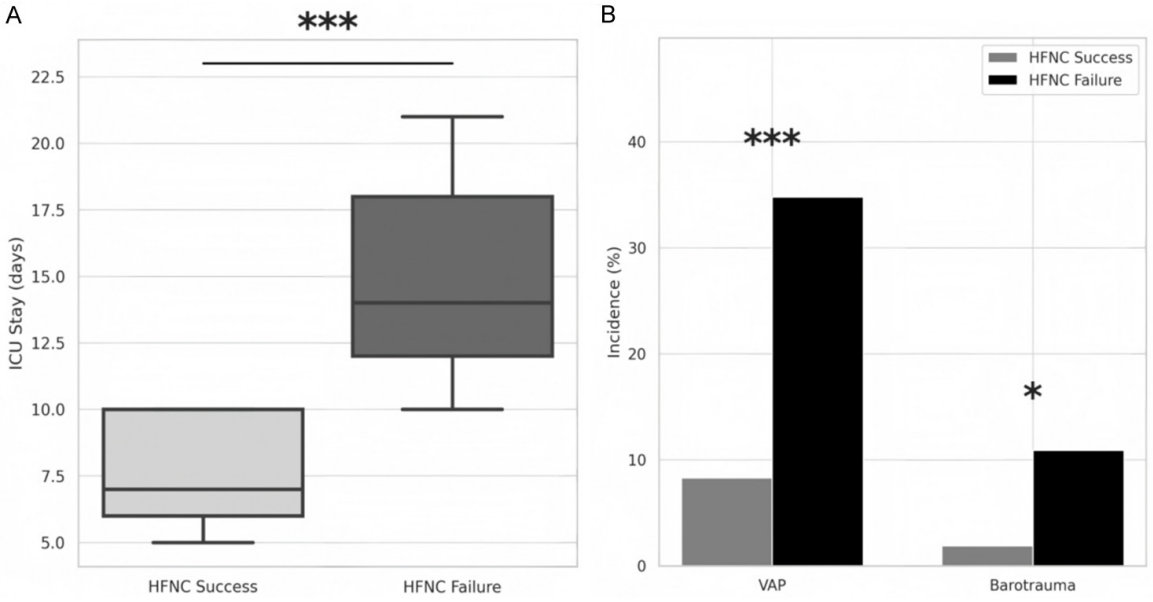

Figure 6. Comparison of intensive care unit (ICU) stay duration and complication incidence between High-Flow Nasal Cannula (HFNC) Success and HFNC Failure groups. A. Box plot showing ICU length of stay (days) in the two groups. Median ICU stay was significantly longer in the HFNC Failure group compared to the HFNC Success group (***P<0.001). B. Bar graph depicting the incidence of ventilator-associated pneumonia (VAP) and barotrauma. The HFNC Failure group had a significantly higher incidence of VAP (***P<0.001) and barotrauma (*P<0.05) than the HFNC Success group.

This study has some limitations. Its single-center, retrospective design inherently introduces selection and information biases. Potential confounding interventions, such as prone positioning or corticosteroid therapy were not controlled for and may have influenced outcomes. Variability in lung compliance measurements between intubated and non-intubated patients could also affect consistency, though standardized regression models were applied for adjustment. Finally, the relatively small sample size may limit the generalizability and statistical power of our findings. Future multicenter prospective studies are warranted to validate our results and explore additional markers such as lung ultrasound scores for enhanced predictive modeling. In conclusion, the combination of lung compliance and $\Delta PaO_2/FiO_2$ improves early identification of HFNC failure and mortality risk, facilitating timely escalation to invasive ventilation.

Disclosure of conflict of interest

None.

Abbreviations

ARDS, Acute Respiratory Distress Syndrome; HFNC, High-Flow Nasal Cannula; PaO_2/FiO_2, Partial Pressure of Arterial Oxygen/Fraction of Inspired Oxygen; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; VAP,

Ventilator-Associated Pneumonia; PEEP, Positive End-Expiratory Pressure; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

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