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# Clinical Outcomes and Predictors of Failure of HFNC Therapy in Acute Hypoxemic Respiratory Failure

*Dr Prateek Achara [1], Dr Jayesh Mittal [2], Dr Mahesh Mawaliya [3], Dr Jitendra singh shekhawat [4], Dr Mohd Irfan [5]*

[1] *Consultant, Dept. of Anaesthesia & Critical care, SBMM heart & critical care Hospital, Sikar, Rajasthan, India*
[2] *Consultant, Dept. of Medicine, SBMM heart & critical care Hospital, Sikar, Rajasthan, India*
[3] *Consultant, Dept. of Medicine, SBMM heart & critical care Hospital, Sikar, Rajasthan, India*
[4] *Assistant professor, Dept. of Anaesthesiology, Tirthankar Mahaveer Medical College And Research Centre, Mooradabaad, Uttar Pradesh, India*
[5] *Junior Resident, Dept. of Medicine, SBMM heart & critical care Hospital, Sikar, Rajasthan, India*

## Corresponding Author

***Dr Mahesh Mawaliya.***
*Consultant, Department of Medicine.*
*SBMM heart & critical care Hospital, Sikar, Rajasthan, India*

**drmaheshmawliya@gmail.com**

## Abstract:

Background: Acute hypoxemic respiratory failure (AHRF) remains a major cause of critical care admission, with timely selection of respiratory support crucial for reducing morbidity and mortality. High-flow nasal cannula (HFNC) therapy has emerged as an effective alternative to conventional oxygen therapy and non-invasive ventilation; however, real-world evidence from Indian clinical settings remains limited. This study evaluated the efficacy of HFNC in AHRF and identified predictors of treatment success and failure.

Methods: This prospective observational study included 296 adult patients with AHRF managed with HFNC in a tertiary care ICU. Baseline demographic and clinical variables, oxygenation indices, early physiological responses (including ROX index at 1 and 6 hours), and HFNC settings were recorded. Patients were categorized into HFNC success (no escalation to invasive mechanical ventilation) and HFNC failure (required intubation). Outcomes included ICU length of stay, ventilator days, and hospital mortality. Statistical comparisons were performed using appropriate parametric and non-parametric tests, with $p < 0.05$ considered significant.

Results: HFNC was successful in 184 patients (62.2%) and failed in 112 (37.8%). Failure was associated with older age (61.1 ± 13.7 vs. 57.7 ± 11.4 years; $p = 0.003$), male predominance (81.3% vs. 58.7%; $p < 0.001$), and a higher prevalence of ARDS (22.3% vs. 12.5%; $p = 0.008$). Baseline severity indicators—including lower $PaO_2/FiO_2$ ratio (152.6 ± 51.3 vs. 181.4 ± 42.4; $p < 0.001$), higher respiratory rate, and higher SOFA scores—were significantly associated with HFNC failure. Early physiological response strongly predicted outcomes: ROX index values at 1 and 6 hours and 24-hour improvement in oxygenation were significantly higher in the success group ($p < 0.001$ for all). HFNC failure resulted in longer ICU stay (10.5 vs. 5.1 days; $p < 0.001$) and higher hospital mortality (28.6% vs. 8.7%; $p < 0.001$). HFNC-related adverse events were infrequent and comparable across groups.

Conclusion: HFNC is an effective and well-tolerated first-line respiratory support modality for AHRF. Early improvements in oxygenation and higher ROX index values are strong predictors of treatment success, whereas older age, ARDS etiology, and greater baseline illness severity are associated with failure. Timely recognition of HFNC non-response is essential to reduce mortality and optimize clinical outcomes.

## Keywords:

High-flow nasal cannula; Acute hypoxemic respiratory failure; ROX index; Predictors of HFNC failure; Mechanical ventilation

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## Introduction

Acute hypoxemic respiratory failure (AHRF) is a major cause of ICU admission worldwide, accounting for nearly 30–40% of all respiratory-related critical care admissions [1]. It is commonly defined as a $PaO_2/FiO_2$ ratio <300 mmHg in the absence of hypercapnia and frequently results from pneumonia, sepsis, acute respiratory distress syndrome (ARDS), and postoperative pulmonary complications [2]. Mortality in AHRF remains high—ranging from 20% to 40% depending on underlying etiology and severity [3]. Early and effective oxygenation strategies are essential to prevent progression to invasive mechanical ventilation (IMV), a transition associated with increased risks of ventilator-associated pneumonia, barotrauma, neuromuscular weakness, and prolonged ICU stay [4].

Conventional oxygen delivery methods (nasal prongs, Venturi masks, and non-rebreather masks) are limited by unpredictable $FiO_2$ delivery, inadequate humidification, and inability to match the patient's high inspiratory demand during respiratory distress. Even at maximum settings, these systems typically provide $FiO_2 \leqslant 0.6$ and flows around 10–15 L/min, which may be insufficient for patients with acute hypoxemia [5]. Non-invasive ventilation (NIV), although widely used, is often associated with mask discomfort, air leaks, gastric insufflation, patient–ventilator dyssynchrony, and failure rates as high as 25–50% in AHRF, particularly in non-hypercapnic etiologies such as pneumonia [6].

High-flow nasal cannula (HFNC) therapy has emerged as an alternative respiratory support modality capable of overcoming many of these limitations. HFNC can deliver up to 60 L/min of warmed, fully humidified gas with precise $FiO_2$ up to 1.0, improving oxygenation and reducing work of breathing [7]. Physiologically, HFNC achieves washing out of nasopharyngeal dead space, generation of low-level positive airway pressure of 2–7 cm $H_2O$ depending on flow and patient breathing pattern, enhanced mucociliary clearance, and reduction in inspiratory resistance [8]. These mechanisms may help stabilize oxygenation and prevent respiratory muscle fatigue, potentially lowering the need for intubation.

Evidence from clinical trials suggests promising outcomes with HFNC. The literature reported significantly lower intubation rates in the HFNC group (38%) compared with standard oxygen therapy (47%) and NIV (50%) in AHRF patients, particularly those with severe hypoxemia ($PaO_2/FiO_2 \leqslant 200$ mmHg) [9]. Furthermore, HFNC demonstrated improved 90-day mortality in this subgroup. Several meta-analyses have since reinforced these findings, showing HFNC to reduce IMV requirement by 10–15% compared with conventional oxygen therapy, with superior patient comfort and lower treatment discontinuation rates [10,11]. However, results remain heterogeneous. Some studies have failed to demonstrate mortality benefit or significant reduction in ICU length of stay, with outcomes influenced by disease etiology, severity of hypoxemia, and timing of HFNC initiation [12].

Importantly, evidence from resource-limited settings is still limited. In many such environments, HFNC was rapidly adopted during the COVID-19 pandemic, yet standardized protocols and real-world evaluations of its effectiveness in non-COVID AHRF remain scarce [13]. Understanding clinical predictors of HFNC success or failure is especially crucial, as delayed recognition of HFNC failure may increase the risk of emergent intubation and associated complications.

Given these uncertainties and the continuing global interest in HFNC, there is a need for context-specific data assessing its efficacy in improving oxygenation, reducing intubation rates, and influencing short-term clinical outcomes in AHRF. Therefore, the present study aimed to evaluate the effectiveness of high-flow oxygen therapy delivered through nasal cannula

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in patients with acute hypoxemic respiratory failure managed at our tertiary care center.

## Material and methods

### Study Design and Setting

This study was designed as a prospective observational study conducted in the Department of Pulmonary and Critical Care Medicine at a tertiary-care teaching hospital. The study was carried out over a period of 12 months, from June 2022 to May 2023, and included all eligible patients admitted with acute hypoxemic respiratory failure (AHRF). The intensive care unit (ICU) is a 20-bed facility equipped with continuous hemodynamic monitoring, ventilatory support systems, and high-flow nasal cannula (HFNC) devices (Fisher & Paykel Optiflow™ ). All patients were managed according to standardized ICU protocols, and no deviations in routine clinical practice were introduced for study purposes.

### Study Population and Eligibility Criteria

Patients were enrolled consecutively based on predefined inclusion and exclusion criteria. Adults aged ⩾18 years presenting with AHRF were eligible if they had a $PaO_2/FiO_2$ ratio <300 mmHg while breathing conventional oxygen therapy and required escalation to HFNC as determined by the treating physician. AHRF was defined as acute onset dyspnea associated with hypoxemia without predominant hypercapnia. Exclusion criteria included patients with primary hypercapnic respiratory failure ($PaCO_2$ >45 mmHg), cardiogenic pulmonary edema, hemodynamic instability requiring high-dose vasopressors, altered mental status with inability to protect airway, do-not-intubate status, immediate need for invasive mechanical ventilation, facial trauma or obstruction precluding nasal interface placement, and pregnancy. Patients who declined participation or had incomplete data were also excluded.

### HFNC Protocol and Clinical Management

All patients received HFNC therapy initiated using a standardized protocol. HFNC was delivered via a heated humidifier system capable of providing flows up to 60 L/min and $FiO_2$ up to 1.0. Therapy was initiated at 40–50 L/min and $FiO_2$ adjusted to maintain $SpO_2$ ⩾ 92%, with higher target values (94–96%) used for non-COPD patients based on physician discretion. Gas temperature was maintained between 34–37°C for optimal humidification and patient comfort. Flow and $FiO_2$ were titrated based on respiratory rate, work of breathing, patient comfort, and arterial blood gas (ABG) parameters. Standard medical therapy including antibiotics, bronchodilators, diuretics, anticoagulation, and corticosteroids was administered depending on underlying etiology of AHRF. All patients were continuously monitored for heart rate, respiratory rate, oxygen saturation, mean arterial pressure, and level of consciousness.

### Assessment of Clinical Response and Criteria for HFNC Failure

Clinical response to HFNC was assessed at baseline, 1 hour, 6 hours, and 24 hours after initiation. Parameters recorded included respiratory rate, $SpO_2$, heart rate, $FiO_2$ requirement, $PaO_2/FiO_2$ ratio, and ROX index ($SpO_2/FiO_2$ divided by respiratory rate). HFNC failure was defined as the need for escalation to non-invasive ventilation or invasive mechanical ventilation due to persistent or worsening hypoxemia, respiratory acidosis, increased work of breathing, hemodynamic instability, or neurological deterioration. The decision for intubation was made by the attending intensivist who was not involved in data analysis, ensuring unbiased clinical judgment.

### Data Collection and Study Variables

Data were collected using a structured proforma by trained ICU personnel. Baseline variables included age, sex, comorbidities, smoking history, and primary diagnosis leading to AHRF. Physiological

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variables included respiratory rate, heart rate, blood pressure, $SpO_2$, ABG values, and severity indices such as the $PaO_2/FiO_2$ ratio and Sequential Organ Failure Assessment (SOFA) score at admission. HFNC-related variables included initial flow, $FiO_2$, temperature settings, and modifications during therapy. Outcome variables included improvement in oxygenation parameters, ROX index at predefined intervals, need for intubation, ICU length of stay, and in-hospital mortality. Adverse events such as nasal dryness, discomfort, or pressure sores were also documented.

**Statistical Analysis**

Data were analyzed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on normality distribution, assessed using the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. Comparisons between HFNC success and failure groups were performed using the Student's t-test or Mann–Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. A p-value <0.05 was considered statistically significant.

**Ethical Considerations**

The study received approval from the Institutional Ethics Committee. Written informed consent was obtained from all patients or their legally authorized representatives prior to inclusion. Patient confidentiality was strictly maintained by anonymizing data and limiting access to study investigators only. The study adhered to the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines.

## Results

A total of 296 patients were included, of whom 184 (62.2%) demonstrated HFNC success while 112 (37.8%) progressed to HFNC failure. Patients in the failure group were significantly older (61.1 ± 13.7 vs. 57.7 ± 11.4 years; $p = 0.003$) and more frequently male (81.3% vs. 58.7%; $p < 0.001$). The prevalence of comorbidities such as diabetes, hypertension, COPD, and smoking history did not differ significantly between groups. Pneumonia was the most common diagnosis (55.7%), followed by ARDS (16.2%), the latter being significantly more common in the failure group (22.3% vs. 12.5%; $p = 0.008$). At baseline, patients who eventually failed HFNC had more severe hypoxemia ($PaO_2/FiO_2$ 152.6 ± 51.3 vs. 181.4 ± 42.4; $p < 0.001$), higher respiratory rates (30.1 ± 6.1 vs. 25.8 ± 4.8 breaths/min; $p < 0.001$), lower $SpO_2$ (86.3 ± 4.2% vs. 89.0 ± 2.8%; $p < 0.001$), and higher SOFA scores (median 7 vs. 5; $p < 0.001$), indicating greater baseline disease severity (Table 1).

*Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (n = 296).*

| Variable | Total (n = 296) | HFNC Success (n = 184) | HFNC Failure (n = 112) | p-value |
|---|---|---|---|---|
| | Frequency (%)/mean ± SD/Median (IQR) | | | |
| Age (years) | 59.0 ± 12.4 | 57.7 ± 11.4 | 61.1 ± 13.7 | 0.003 |
| Gender | | | | |
| Female | 93 (32.8%) | 76 (41.3%) | 21 (18.7%) | <0.001 |
| Male | 199 (67.2%) | 108 (58.7%) | 91 (81.3%) | |
| Comorbities | | | | |
| Diabetes | 126 (42.6%) | 77 (41.8%) | 49 (43.8%) | 0.842 |

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|---|---|---|---|---|
| **Hypertension** | **153 (51.7%)** | **95 (51.6%)** | **58 (51.8%)** | **0.996** |
| **COPD** | **29 (9.8%)** | **20 (10.9%)** | **9 (8.0%)** | **0.553** |
| **Current smoker** | **86 (29.1%)** | **47 (25.5%)** | **39 (34.8%)** | **0.116** |
| **Primary diagnosis** | | | | |
| **Pneumonia** | **165 (55.7%)** | **100 (54.3%)** | **65 (58.0%)** | **0.405** |
| **ARDS** | **48 (16.2%)** | **23 (12.5%)** | **25 (22.3%)** | **0.008** |
| **Sepsis (non-pulmonary)** | **43 (14.5%)** | **30 (16.3%)** | **13 (11.6%)** | **0.361** |
| **Post-op pulmonary complication** | **17 (5.7%)** | **14 (7.6%)** | **3 (2.7%)** | **0.055** |
| **Aspiration** | **7 (2.4%)** | **4 (2.2%)** | **3 (2.7%)** | **0.674** |
| **Others** | **16 (5.4%)** | **13 (7.1%)** | **3 (2.7%)** | **0.076** |
| **Baseline $PaO_2/FiO_2$ (mmHg)** | **170.5 ± 47.9** | **181.4 ± 42.4** | **152.6 ± 51.3** | **<0.001** |
| **Respiratory rate (breaths/min)** | **27.4 ± 5.7** | **25.8 ± 4.8** | **30.1 ± 6.1** | **<0.001** |
| **$SpO_2$ (%) on admission** | **88.0 ± 3.7** | **89.0 ± 2.8** | **86.3 ± 4.2** | **<0.001** |
| **SOFA score** | **5 (4–7)** | **5 (3–6)** | **7 (5–8.25)** | **<0.001** |

HFNC was initiated at similar flow rates across both groups (median 45 L/min), although the difference in overall distribution was statistically significant ($p < 0.001$). Patients who failed HFNC required substantially higher initial $FiO_2$ (0.73 vs. 0.61; $p < 0.001$). At 24 hours, oxygenation improved markedly in the success group, with $PaO_2/FiO_2$ rising from baseline to 241.4 ± 50.4 mmHg compared with only 137.6 ± 55.2 mmHg in the failure group ($p < 0.001$). The mean change in $PaO_2/FiO_2$ showed a positive trajectory in the success group (+60.0 ± 25.3) but worsened in the failure group (−15.0 ± 34.9; $p < 0.001$). Similarly, ROX indices at both 1 hour and 6 hours were significantly higher among HFNC successes ($p < 0.001$ for both time points), indicating better early physiologic response and predictive value for HFNC outcomes (Table 2).

*Table 2. HFNC Settings and Early Physiologic Response.*

| Variable | Total (n = 296) | HFNC Success (n = 184) | HFNC Failure (n = 112) | p-value |
|---|---|---|---|---|
| | mean ± SD/Median (IQR) | | | |
| **Initial HFNC flow (L/min)** | **45** | **45** | **45** | **<0.001** |
| **Initial $FiO_2$** | **0.66 (0.56–0.73)** | **0.61 (0.54–0.69)** | **0.73 (0.66–0.85)** | **<0.001** |
| **$PaO_2/FiO_2$ at 24 hour (mmHg)** | **204.3 ± 66.1** | **241.4 ± 50.4** | **137.6 ± 55.2** | **<0.001** |
| **Change in $PaO_2/FiO_2$ (baseline → 24 hour)** | **+33.9 ± 48.7** | **+60.0 ± 25.3** | **−15.0 ± 34.9** | **<0.001** |
| **ROX index at 1 hour** | **0.050 (0.041–0.063)** | **0.058 (0.049–0.069)** | **0.040 (0.032–0.046)** | **<0.001** |
| **ROX index at 6 hour** | **0.065 (0.037–0.083)** | **0.078 (0.067–0.092)** | **0.031 (0.017–0.043)** | **<0.001** |

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Clinical outcomes differed markedly between the two groups. All patients in the failure group required intubation (112/112; 100%), whereas none in the success group progressed to invasive mechanical ventilation. HFNC failure was also associated with a significantly longer ICU stay (median 10.5 vs. 5.1 days; $p < 0.001$) and a median ventilator duration of 7.0 days among those intubated. Hospital mortality was significantly higher in the failure group (28.6% vs. 8.7%; $p < 0.001$). Adverse events related to HFNC interface use—such as nasal dryness (10.9% vs. 14.3%) and pressure injury (1.6% vs. 3.6%)—were infrequent and comparable between groups, with no statistically significant differences (Table 3).

*Table 3. Clinical Outcomes Among HFNC Success and Failure Groups.*

| Outcome | HFNC Success (n = 184) | HFNC Failure (n = 112) | p-value |
|---|---|---|---|
| | Frequency (%)Median (IQR) | | |
| Required intubation | 0 (0.0%) | 112 (100.0%) | — |
| ICU length of stays (days) | 5.1 (3.3–6.5) | 10.5 (6.2–13.9) | <0.001 |
| Ventilator days | — | 7.0 (4.3–9.5) | — |
| Hospital mortality | 16 (8.7%) | 32 (28.6%) | <0.001 |
| Nasal dryness | 20 (10.9%) | 16 (14.3%) | 0.409 |
| Nasal pressure injury | 3 (1.6%) | 4 (3.6%) | 0.512 |

## Discussion

In this prospective observational study of 296 patients with acute hypoxemic respiratory failure (AHRF), we found that high-flow nasal cannula (HFNC) therapy was successful in approximately two-thirds of patients (62.2%), a proportion consistent with prior reports by Chavarria et al., Long et al., and Zhao et al., ranging from 55–70% in similar populations [14,15,16]. Our results further demonstrate that baseline patient characteristics, severity of hypoxemia, and early physiological response to HFNC were strong predictors of treatment success, aligning with existing evidence and reinforcing the clinical utility of HFNC in AHRF [17].

Patients who failed HFNC were significantly older and predominantly male, a pattern that parallels previous studies showing higher HFNC failure rates in the elderly due to reduced physiologic reserve, impaired ventilatory mechanics, and higher comorbidity burden [18,19]. Although comorbidities such as diabetes, hypertension, and COPD did not differ between groups, the higher prevalence of ARDS in the failure group (22.3% vs. 12.5%; $p = 0.008$) is clinically consistent with ARDS being a strong predictor of HFNC non-response owing to extensive alveolar injury and severe ventilation–perfusion mismatch. Similar associations have been highlighted in the work of He et al., and Wang et al., where ARDS patients demonstrated higher intubation rates despite HFNC [20,21].

Baseline oxygenation indices in our cohort were strongly predictive of outcomes. Patients in the failure group had significantly lower baseline $PaO_2/FiO_2$ ratios (152.6 vs. 181.4 mmHg; $p < 0.001$), higher respiratory rates, and higher SOFA scores, all markers of more severe respiratory and systemic illness. This mirrors findings from the Scala et al., study and subsequent meta-analyses by Leeies et al., showing that $PaO_2/FiO_2 < 150$ mmHg is a critical threshold beyond which HFNC failure becomes more likely [22,23]. The physiological basis for this lies in refractory hypoxemia where HFNC's benefits

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dead-space washout, improved humidification, modest positive airway pressure may be insufficient to compensate for severe parenchymal disease [17].

A key strength of our study is the detailed assessment of early physiological response to HFNC [17]. At both 1 and 6 hours, ROX index values were significantly higher in the success group ($p < 0.001$), reflecting more favorable respiratory mechanics and oxygenation. Patients who failed HFNC not only required higher $FiO_2$ at initiation (0.73 vs. 0.61) but demonstrated a decline in $PaO_2/FiO_2$ at 24 hours (−15.0 vs. +60.0 mmHg). These findings are congruent with the seminal work by Praphruetkit et al., who demonstrated that a ROX index < 3.85 at 12 hours strongly predicts HFNC failure [24]. Although our absolute ROX values appear numerically lower due to formula scaling differences, the directional trends and discriminative ability remain consistent with prior literature [25,26]. Early improvement in oxygenation is key because HFNC promotes alveolar recruitment, reduces inspiratory effort, and delivers stable $FiO_2$; lack of improvement suggests underlying severity that exceeds HFNC's physiological support [28].

Clinical outcomes in our study further underscore the importance of timely identification of HFNC failure. All patients in the failure group progressed to intubation, with significantly longer ICU stays (10.5 vs. 5.1 days) and markedly higher hospital mortality (28.6% vs. 8.7%; $p < 0.001$). This aligns with study by Kang et al., which found that delayed intubation in HFNC non-responders is independently associated with higher mortality [29]. The median ventilator duration of seven days in our failure group also reflects typical trajectories for severe respiratory failure requiring mechanical ventilation in Indian tertiary ICUs [30]. Importantly, HFNC-related adverse events were rare and comparable between groups, reaffirming HFNC's favorable safety and tolerability profile, one of its major advantages over non-invasive ventilation [31].

## Limitations

This study has several limitations. As an observational study, residual confounding cannot be completely excluded, and causality cannot be inferred. Although HFNC initiation followed a standardized protocol, decisions regarding intubation were clinician-dependent and may have introduced subjective variability. ROX index values could not be assessed beyond 6 hours for all patients due to logistical constraints, limiting analysis of its predictive trajectory. The single-center design may also affect generalizability to other healthcare settings with differing patient profiles or HFNC practices. Finally, underlying etiological heterogeneity—particularly among ARDS and pneumonia cases—may influence response patterns in ways not fully captured in subgroup analyses.

## Conclusion

In this prospective study of patients with acute hypoxemic respiratory failure, high-flow nasal cannula therapy demonstrated a success rate of 62.2%, with favorable outcomes strongly associated with less severe baseline hypoxemia, lower respiratory effort, and a more robust early physiological response. Early improvements in oxygenation and higher ROX index values were consistent predictors of HFNC success, whereas older age, male gender, higher SOFA scores, and ARDS etiology were linked to failure and subsequent need for intubation. HFNC failure was associated with significantly longer ICU stays and higher mortality, underscoring the importance of timely recognition of non-response. Overall, our findings support the use of HFNC as an effective and well-tolerated first-line modality in managing acute hypoxemic respiratory failure, while also highlighting key clinical indicators that may guide early escalation to invasive mechanical ventilation. These results add to the growing evidence base and provide valuable context-specific insights for clinical decision-making in Indian critical care settings.

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