ORIGINAL ARTICLE

# High-flow Nasal Oxygen Therapy in COVID-19 Critically Ill Patients with Acute Hypoxemic Respiratory Failure: A Prospective Observational Cohort Study

Mohd Saif Khan[1], Jay Prakash[2], Sudipto Banerjee[3], Pradip K Bhattacharya[4], Raman Kumar[5], Deepak K Nirala[6]

## Abstract

**Background:** Coronavirus disease-2019 (COVID-19) is prone to acute hypoxemic respiratory failure (AHRF). Because tracheal intubation is associated with a higher risk of death in these patients, AHRF employs high-flow nasal oxygen therapy (HFNOT). The goal of this study was to assess the effect of HFNOT on oxygenation status as well as different predictors of HFNOT failure.

**Methods:** A prospective observational cohort study was conducted in COVID-positive critically ill adult patients (age >18 years) with AHRF, who were unable to maintain $SpO_2$ >90% on a non-rebreathing face mask at an oxygen flow ≥15 L/minute. Respiratory variables ($PaO_2/FiO_2$, $SpO_2$, and RR) before HFNOT (baseline) and then at 1 hour, 6 hours, 7th day, and 14th day after HFNOT application were recorded. Borg CR10 scale and visual analogue scale were used to evaluate the subjective sensation of dyspnea and comfort level, respectively. As needed, Student's *t*, Mann–Whitney *U*, or Wilcoxon signed-rank tests were performed. To find parameters linked to HFNOT failure, multivariate logistic regression and receiver-operating characteristic (ROC) analysis were employed.

**Results:** A total of 114 patients were enrolled in the study, with an HFNOT failure rate of 29%. The median $PaO_2/FiO_2$ ratio at baseline (before the initiation of HFNOT) was 99.5 (80–110) which significantly increased at various time points (1 hour, 6 hours, 7th day, and 14th day) after HFNOT initiation in the successful group. Patients reported significant improvement in sensation of breathlessness [9 (8–10), 3 (2–4); $p$ <0.001] as well as in comfort level [2 (1–2), 8 (4–9); $p$ <0.001]. Multivariate logistic regression analysis, sequential organ failure assessment (SOFA) score >7, acute physiology and chronic health evaluation (APACHE) II score >20, admission P/F ratio <100, D-dimer >2 mg/L, IL-6 >40 pg/mL, random blood sugar (RBS) >250 mg/dL, and 6 hours ROX Index <3.5 were independent prognostic factors of HFNOT failure.

**Conclusion:** The use of HFNOT significantly increased the oxygenation levels in COVID-19 patients with AHRF at various time periods after HFNOT beginning. Age, SOFA score, APACHE II score, ROX score, admission P/F ratio, IL-6, D-dimer, and RBS were independent prognostic factors of HFNOT failure in this cohort.

**Keywords:** Acute hypoxemic respiratory failure, COVID-19, High-flow nasal oxygen therapy.

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## Introduction

In December 2019, a deadly disease caused by the novel coronavirus (SARS-CoV-2) emerged in Wuhan, China, which was termed as "coronavirus disease-2019 (COVID-19)" by the World Health Organization in the International Classification of Diseases (ICD).[1] Virus enters into the lung through the inhalation route and infects lung parenchyma to cause severe COVID-19 pneumonia in 14% of cases.[2] About 15.6–31% of COVID-19 patients develop acute respiratory distress syndrome (ARDS),[3] which is clinically characterized by acute onset of dyspnea, hypoxemia, and appearance of bilateral diffuse radiological infiltrates.[4] Although the exact mechanisms by which SARS-CoV-2 causes lung damage are unknown, possible contributors include a cytokine release issue triggered by viral antigen, drug-induced pulmonary toxicity, high airway pressure, and hyperoxia-induced severe lung damage after mechanical ventilation.[5] COVID-19 is a systemic illness caused by widespread endothelial injury.[6] Hypoxemia in COVID-19 ARDS occurs due to the presence of intrapulmonary ventilation-perfusion mismatch or shunt. Such patients most benefit from oxygen delivery devices which may be invasive or noninvasive. Invasive oxygen device (i.e., mechanical ventilator) requires tracheal intubation, which eventually carries a considerable risk of complications (intensive care acquired weakness, ventilator-associated pneumonia, ventilator dependence, ICU delirium) and mortality (61–96%).[7,8]

The use of noninvasive oxygen delivery devices, which include noninvasive ventilation (NIV) and HFNOT, has become routine. Nonetheless, there were concerns about the use of NIV and HFNOT during the early stages of the pandemic because of the possibility of aerosolization and exposure to clinical staff.[9] But, the subsequent

[1–6]Department of Critical Care Medicine, Rajendra Institute Medical Sciences, Ranchi, Jharkhand, India

**Corresponding Author:** Jay Prakash, Department of Critical Care Medicine, Rajendra Institute Medical Sciences, Ranchi, Jharkhand, India, Phone: +91 8084715507, e-mail: dr.jay_prakash@rediffmail.com

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investigation showed only limited exposure risks with the use of such devices, and therefore, NIV and HFNOT both are being used in COVID-19 ARDS.[10] NIV has various drawbacks such as patient intolerance due to discomfort and claustrophobia, mask leak and patient-ventilator asynchrony, patient self-induced lung injury, and inability to maintain oral hygiene. HFNOT, on the contrary, has been shown to reduce the progression to invasive mechanical ventilation (IMV), compared with other types of noninvasive oxygen therapy.[11,12] In a recent prospective multicentre cohort study on 122 matched patients, in comparison with early intubation, HFNOT increased ventilator-free days by 8 days.[13] Therefore, HFNOT may be considered as initial respiratory support of choice in COVID-19 ARDS. A limited number of studies exploring the impact of HFNOT in COVID-19 pneumonia have been performed, albeit with small sample sizes.[14–16] Therefore, we planned this study with an aim to determine the impact of HFNOT on the oxygenation level in COVID-19 critically ill patients presenting with acute hypoxemic respiratory failure (AHRF). Primary objective was to record the change in $PaO_2/FiO_2$ ratio from baseline to various time points (1 hour, 6 hours, 7th day, and 14th day) after the initiation of HFNOT. The secondary objective was to determine the factors that predict HFNOT failure (i.e., requirement of IMV or NIV).

## Materials and Methods

### Study Design and Setting

A prospective observational cohort study was conducted with written informed consent from enrolled patients admitted to a designated COVID intensive care unit (ICU) at a tertiary care hospital in East India after obtaining approvals from the Institutional Ethics Committee (IEC). All data were collected from clinical records. The trial registration was done with Clinical Trial Registry India (CTRI/2020/10/028634). This study was performed in accordance with guidelines set by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Patients admitted between November 2020 and February 2021 were included who satisfied the following inclusion criteria: COVID-positive status (SARS-CoV-2 detected in nasopharyngeal swab by real-time reverse transcription-polymerase chain reaction assay), critically ill adult (aged ≥18 years) patients, presence of AHRF (defined as $PaO_2/FiO_2$ ratio <300 or peripheral oxygen saturation <90% with respiratory rate >25 breaths per minute), and inability to maintain peripheral oxygen saturation ≥90% on standard oxygen therapy (non-rebreathing face mask) at oxygen flow rate ≥15 L/minute. Patients with age <18 years, tracheal intubation or NIV use prior to HFNOT, and hemodynamic shock (defined as SBP <90 mm Hg or mean arterial pressure <65 mm Hg or requirement of vasopressor) were excluded.

### HFNOT Protocol

On HFNOT device (AIRVO™-2, Fisher & Paykel Healthcare Corporation Limited, Auckland, New Zealand), initial flow rates and $FiO_2$ were set at 50–60 L/minute and 80–100%, respectively. $FiO_2$ was later down-titrated to attain the target $SpO_2$ of just above 90%. Inspiratory flow rates were adjusted to match the patient's inspiratory demand as manifested by clinical findings of respiratory failure (respiratory rate >25/minute, use of accessory muscles of respiration and perspiration). During HFNOT, patients were also instructed to lie down in a prone position for 2 hours/session with three to four such sessions per day. They were also instructed to perform incentive spirometry every 3–4 hourly and steam inhalation 8 hourly.

Initially, HFNOT was used continuously; however, a patient's respiratory distress disappeared; HFNOT was gradually weaned off using a protocol (increasing the time of venturi mask trials while stepwise decreasing $FiO_2$ levels and flows). Higher respiratory support (NIV or IMV) was employed to improve respiratory parameters in cases of respiratory deterioration or nonresponders. HFNOT failure was defined by the need of NIV or IMV as rescue therapy.

### Data Collection and Study Variables

On a predesigned and printed case record form (CRF), demographic characteristics, acute physiology and chronic health evaluation (APACHE II) and sequential organ failure assessment (SOFA) scores, vital signs, and laboratory and arterial blood gas parameters were sequentially entered. We collected respiratory variables such as $PaO_2/FiO_2$, $SpO_2$, and RR before HFNOT (baseline) and later at 1 hour, 6 hours, 7th day, and 14th day after HFNOT application. The ROX index (ratio of $SpO_2/FiO_2$ to RR) was calculated at 2 and 6 hours of HFNOT. The subjective sensation of dyspnea was assessed using the Borg CR10 scale (from 0 to 10—maximum dyspnea), and the level of comfort was assessed using a visual analogue scale (from 1—very uncomfortable to 10—very comfortable); both scores were recorded before (baseline) and 1 hour after HFNOT initiation. All patients were followed up till Day 28 or death, whichever was earlier.

### Statistical Analysis

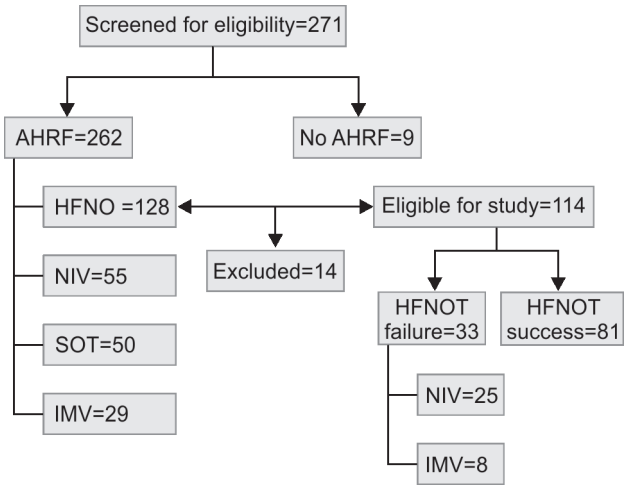
Continuous data were expressed as mean ± standard deviation or median with interquartile ranges (25th and 75th percentiles), depending upon skewness of distribution of data. To determine the normality of the data distribution, the Shapiro–Wilk test was used. Dichotomous data were reported as numbers (percentage) and analyzed using Fisher's exact test. The intergroup differences were analyzed using Student's *t* test or Mann–Whitney *U* test. The intragroup differences between variables at different time points were compared using the Friedman test and the Wilcoxon signed-rank test. Univariate analysis was performed to select statistically significant variables associated with HFNOT failure; these variables were entered in a stepwise logistic regression analysis to determine factors associated with HFNOT failure. Receiver operating characteristic (ROC) analysis was performed, and the areas under the ROC curve (AUROC) were calculated to identify the best predictor of HFNOT failure. All statistical tests were two-tailed,and statistical significance was considered as a $p$-value ≤0.05. All statistical analyses were run on Statistical Package for Social Sciences (SPSS) software (version 20.0; IBM, Armonk, New York, USA).

## Results

A total of 271 patients were screened during study period, out of which 262 patients had AHRF, and HFNOT was used as first-line therapy in 128 patients. Finally, 114 patients were included in the study, out of which 33 patients (29%) failed to tolerate HFNOT, resulting in escalation to either NIV (25 patients) or IMV (8 patients) (Flowchart 1).

Demographic characteristics and clinical and laboratory parameters between HFNOT success and failure groups of all included patients ($n$ = 114) as shown in Table 1. The mean age of the patients was 60.3 ± 14.4 years which was significantly higher in HFNOT failure than that of HFNOT success group ($p$ <0.001). Male patients accounted for the majority (81%) of HFNOT cohort. Key comorbidities were diabetes mellitus (50%), hypertension

**Flowchart 1:** Flowchart of subject screening and eligibility and allocation to various oxygen support devices




(26%), and chronic kidney disease (8%). The majority of patients required therapeutic anticoagulation (81%), whereas the rest were on prophylactic anticoagulants. All patients were given IV dexamethasone 6 mg/day. About 90% of patients received intravenous remdesivir. Twenty-three patients (20%) had a high procalcitonin value (2 ng/mL) and hence required escalation of antibacterial therapy. The median $PaO_2/FiO_2$ ratio at baseline (before the initiation of HFNOT) was 99.5 (80–110) which gradually and significantly increased at various time points (1 hour, 6 hours, 7th day, and 14th day) after HFNOT initiation in the successful group (Fig. 1, Table 2). This improvement was found to be significantly higher in HFNOT success group compared to failure group (Fig. 1, Table 2).

Patients reported significant improvement in sensation of breathlessness as well as in comfort level after application of HFNOT. This improvement was more in the HFNOT success group compared to the failure group (Fig. 2, Table 3).

It was observed that compared to successful group, the HFNOT failure group was significantly older (70.7 ± 10.7, 56 ± 13.6, $p$ <0.001),

**Table 1:** Comparisons of demographic, clinical, and laboratory parameters between HFNOT success and failure groups

| *Parameters* | *All (n = 114)* | *HFNOT success group (n = 81)* | *HFNOT failure group (n = 33)* | *p value* |
|---|---|---|---|---|
| Age (years), mean ± SD | 60.3 ± 14.4 | 56 ± 13.6 | 70.7 ± 10.7 | <0.001 |
| Male, *n* (%) | 92 (80.7) | 64 (79.0) | 28 (84.8) | 0.472 |
| Comorbidities | | | | |
| Hypertension, *n* (%) | 30 (26.3) | 21 (25.9) | 9 (27.3) | 0.881 |
| Diabetes mellitus, *n* (%) | 57 (50) | 41 (50.6) | 16 (48.5) | 0.834 |
| Chronic kidney disease, *n* (%) | 9 (7.9) | 5 (6.2) | 4 (12.1) | 0.285 |
| APACHE II score, mean ± SD | 15.1 ± 4.6 | 12.4 ± 1.8 | 21.6 ± 2.1 | <0.001 |
| SOFA score, mean ± SD | 6.5 ± 1.9 | 5.5 ± 0.9 | 9.2 ± 0.9 | <0.001 |
| Duration of symptoms before HFNOT (days), mean ± SD | 5.9 ± 2.1 | 4.9 ± 1.4 | 8.3 ± 1.5 | <0.001 |
| Duration of HFNOT (days), mean ± SD | 9.1 ± 3.7 | 10.7 ± 2.3 | 5.2 ± 3.7 | <0.001 |
| ICU LOS (days), mean ± SD | 15.4 ± 4.8 | 16.7 ± 3.2 | 12.0 ± 6.3 | <0.001 |
| Prone positioning | 41 (35.9) | 35 (43.2) | 6 (18.2) | 0.0114 |
| Use of steroids, *n* (%) | 110 (96.5) | 77 (95.1) | 33 (100) | 0.1936 |
| Use of remdesivir, *n* (%) | 102 (90) | 72 (88.9) | 30 (90.9) | 0.7533 |
| Vitals before HFNOT: | | | | |
| HR (beats/minute), mean ± SD | 113.5 ± 14 | 111 ± 12.7 | 119 ± 15.7 | 0.006 |
| MAP (mm Hg), mean ± SD | 69 (65–78) | 69 (65–78) | 67 (60–78) | 0.700 |
| RR (breaths/minute), median (IQR) | 34 (31–35) | 33 (31–35) | 34 (32–39) | 0.203 |
| $PaCO_2$, median (IQR) | 40 (32–45) | 40 (34–45) | 40 (31–45) | 0.411 |
| $SpO_2$ (%), median (IQR) | 78 (65–84) | 80 (65–87) | 66 (60–73) | <0.001 |
| $PaO_2/FiO_2$ ratio, mean ± SD | 97 ± 29.2 | 103.4 ± 29.3 | 81.4 ± 22.5 | 0.001 |
| $PaO_2/FiO_2$ ≤100, *n* (%) | 73 (64.0) | 46 (56.8) | 27 (81.8) | 0.0114 |
| ROX index (at 1 hour), mean ± SD | 3.2 ± 0.5 | 3.4 ± 0.4 | 2.8 ± 0.4 | <0.001 |
| ROX index (at 6 hours), mean ± SD | 4.0 ± 1.1 | 4.4 ± 0.9 | 3.0 ± 0.5 | <0.001 |
| D-dimer (mg/L), mean ± SD | 1.7 ± 1.00 | 1.2 ± 0.6 | 3.0 ± 0.7 | <0.001 |
| IL-6 (pg/mL), median (IQR) | 26 (17–48) | 23 (14–29) | 67 (47–91) | <0.001 |
| RBS (mg/dL), mean ± SD | 222.1 ± 107.5 | 176.4 ± 71.5 | 334.2 ± 99.0 | <0.001 |
| ICU mortality, *n* (%) | 20 (17.5) | 0 (0) | 20 (60.6) | <0.001 |
| 28-day mortality, *n* (%) | 31 (27.2) | 0 (0) | 31 (93.9) | <0.001 |

HFNOT, high-flow nasal oxygen therapy; IL-6, interleukin-6; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; ROX index, respiratory rate-oxygenation index; RBS, random blood sugar; $PaO_2$, partial pressure of oxygen in arterial blood; $FiO_2$, fraction of inspired oxygen concentration; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate

with lower baseline median $SpO_2$ [66 (60–73), 80 (67.5–87); $p$ <0.001], lower baseline median P/F ratio [87 (65.5–100), 100 (89.5–110); $p$ <0.001], lower mean ROX index at 1 hour (2.8 ± 0.4, 3.4 ± 0.4; $p$ <0.001) and 6 hours (3.0 ± 0.5, 4.4 ± 0.9; $p$ <0.001), higher median heart rates (119 ± 15.7, 111 ± 12.7; $p$ <0.001), higher APACHE II (21.6 ± 2.1, 12.4 ± 1.8; $p$ <0.001) and SOFA scores (9.2 ± 0.9, 5.5 ± 0.9; $p$ <0.001), and higher values of IL-6, D-dimer, and random blood sugar (RBS) levels (Table 1). On univariate analysis, age >65 years, APACHE II >20, SOFA >7, 2-hour ROX index, 6-hour ROX index, baseline P/F ratio, $SpO_2$ <70%, D-dimer >2 mg/L, IL-6 >40 pg/mL, RBS >250 mg/dL, and absence of prone positioning were statistically significant factors (odds ratio >1, $p$ <0.05) contributing to the HFNOT failure (Table 4). After incorporating all these factors related to HFNOT failure into multivariate logistic regression analysis, we found that age >65 years, SOFA >7, APACHE II >20, admission P/F ratio <100, $SpO_2$ <70%, HR >120 bpm, D-dimer >2 mg/L, IL-6 >40 pg/mL, RBS >250 mg/dL, 6-hour ROX index <3.5, and 1-hour ROX index <3, were independent prognostic factors of HFNOT failure. Further, on ROC analysis, we found highest AUROCs with APACHE II score, SOFA score, D-dimer, ROX index at 6 hours and 1 hour, IL-6, and RBS. Among these indicators, the APACHE II greater than 20 was the most relevant predictor of HFNOT failure (Table 4, Figs 3A and B).

Complications specific to HFNOT application were noted in 50.9% of patients, in which epistaxis (18.4%) and air hunger (15.7%) were the most common complications (Table 5). However, one patient developed spontaneous tension pneumothorax which required immediate intercostal drain tube placement following which the patient dramatically improved and survived to hospital discharge.

## Discussion

This study, which was conducted to evaluate the impact of HFNOT in COVID-19 critically ill patients who developed severe

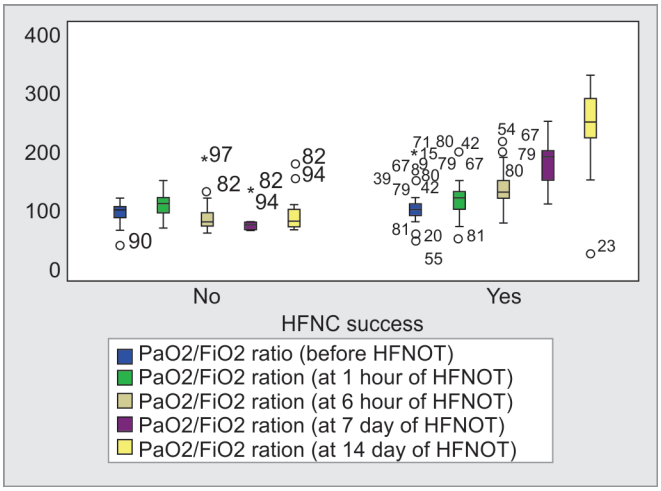



**Fig. 1:** Box plots of median (IQR) $PaO_2/FiO_2$ ratios at various time points in HFNOT success and failure groups

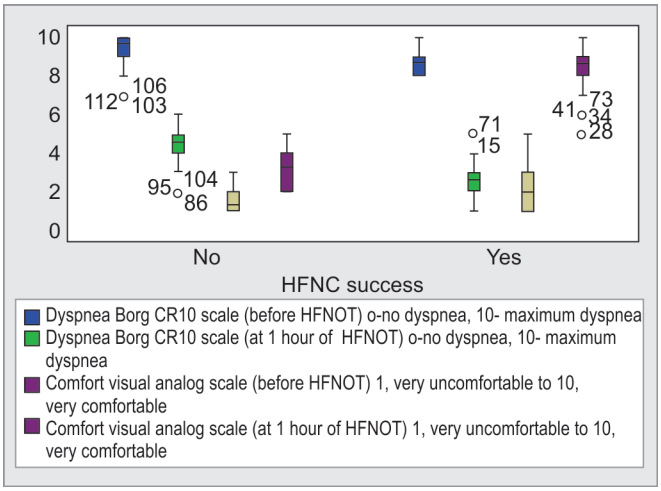



**Fig. 2:** Box plots of dyspnea Borg scale and comfort VAS of HFNOT success and failure groups

**Table 2:** Change in respiratory parameters from baseline (after the initiation of HFNOT) to various time points (1 hour, 6 hours, 7th day and 14th day) after the initiation of HFNOT in success and failure groups

| | *Time points* | *All patients (n = 114)* | *HFNOT success (n = 81)* | *HFNOT failure (n = 33)* | *p value*[†] |
|---|---|---|---|---|---|
| $PaO_2/FiO_2$ ratio | Baseline | 99.5 (80–110) | 100 (89.5–110) | 87 (65.5–100) | <0.001 |
| | 1 hour | 114 (100–130) | 120 (100–140) | 100 (84.5–120) | <0.001 |
| | 6 hours | 126 (97.75–143.25) | 130 (120–153.5) | 81 (69–96.5) | <0.001 |
| | 7th day | 170 (129–200) | 192 (150–201) | 67 (66–79) | <0.001 |
| | 14th day | 250 (199.50–281.75) | 250 (221–290) | 80 (70–105) | <0.001 |
| *p* value[‡] | | <0.001 | <0.001 | <0.001 | |
| Respiratory rate | Baseline | 34 (31–35) | 33 (31–35) | 34 (32–37) | 0.203 |
| | 1 hour | 30 (28–32) | 30 (26.5–30) | 33 (32–35) | <0.001 |
| | 6 hours | 29.5 (28–30) | 29 (28–30) | 30 (28.5–33) | 0.006 |
| | 7th day | 24 (22–28) | 24 (22–26) | 28 (22–32.25) | <0.001 |
| | 14th day | 24 (22–26) | 22 (18–23) | 27 (24–30) | <0.001 |
| *p* value[‡] | | <0.001 | <0.001 | <0.001 | |
| $SpO_2$ | Baseline | 78 (65.75–84) | 80 (67.5–87) | 66 (60–73) | <0.001 |
| | 1 hour | 94 (91–98) | 96 (92–99) | 91 (90–92) | <0.001 |
| | 6 hours | 94 (91–97) | 95 (92–97.5) | 90 (89–95.5) | <0.001 |
| | 7th day | 97 (92–98) | 98 (96–98) | 89.5 (85–90) | <0.001 |
| | 14th day | 98 (95–99) | 98 (97–99) | 86.5 (85–90.75) | <0.001 |
| *p* value[‡] | | <0.001 | <0.001 | <0.001 | |

[†]Mann–Whitney *U*-test, [‡]Friedman test; all values are expressed as median (25–75% inter quartile range)

**Table 3:** Dyspnea Borg scale and comfort VAS among between HFNOT success and failure groups

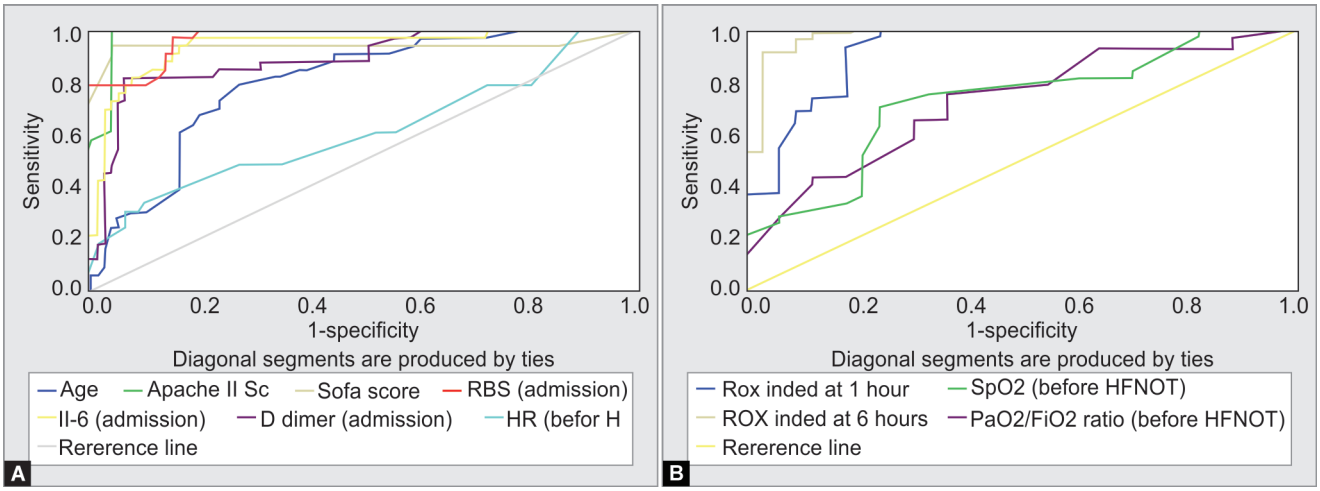
| | *All patients* | *HFNOT success (n = 81)* | *HFNOT failure (n = 33)* | *p value*[†] |
|---|---|---|---|---|
| Dyspnea Borg scale (baseline) | 9 (8–10) | 9 (8–9) | 10 (9–10) | <0.001 |
| Dyspnea Borg scale (after 1-hour HFNOT) | 3 (2–4) | 3 (2–3) | 4 (4–5) | <0.001 |
| *p* value[‡] | <0.001 | <0.001 | <0.001 | |
| Comfort VAS (baseline) | 2 (1–2) | 2 (1–3) | 2 (1–2) | <0.001 |
| Comfort VAS (after 1-hour HFNOT) | 8 (4–9) | 9 (8–9) | 3 (2–4) | <0.001 |
| *p* value[‡] | <0.001 | <0.001 | <0.001 | |

[†]Mann—Whitney *U*-test between HFNOT failure and success groups; [‡]Wilcoxon signed-rank test between variables at two time points in same group; all values are expressed as median (25–75% inter quartile range)

**Table 4:** Predictors of HFNOT failure using multivariate logistic regression analysis and ROC analysis

| *Variables* | *Univariate analysis (OR with 95% CI)* | *p value* | *Multivariate analysis (OR)* | *p value* | *AUROC (95% CI)* | *p value* |
|---|---|---|---|---|---|---|
| Age >65 years | 8.70 (3.46–21.89) | <0.001 | 8.43 | <0.001 | 0.801 (0.717–0.885) | <0.001 |
| APACHE II score >20 | 40.00 (10.38–154.00) | <0.001 | 16.20 | <0.001 | 0.985 (0.967–1.000) | <0.001 |
| SOFA >7 | 260.00 (49.70–1360.33) | <0.001 | 78.00 | <0.001 | 0.935 (0.864–1.000) | <0.001 |
| P/F ratio <100 | 3.42 (1.28–9.20) | 0.0146 | 5.83 | <0.001 | 0.723 (0.623–0.823) | <0.001 |
| 1-hour ROX index <3 | 68.40 (19.30–242.46) | <0.001 | 15.20 | <0.001 | 0.922 (0.860–0.984) | <0.001 |
| Admission $SpO_2$ <70% | 5.92 (2.36–14.82) | <0.001 | | <0.001 | 0.726 (0.624–0.828) | <0.001 |
| 6-hour ROX index <3.5 | 260.00 (49.69–1360.33) | <0.001 | 25.67 | <0.001 | 0.978 (0.949–1.000) | <0.001 |
| Admission D-dimer >2 mg/L | 63.64 (16.56–244.58) | <0.001 | 23.33 | <0.001 | 0.970 (0.944–0.996) | <0.001 |
| Admission RBS >250 mg/dL | 15.75 (5.63–44.03) | <0.001 | 10.50 | <0.001 | 0.893 (0.826–0.961) | <0.001 |
| Admission IL-6 >40 pg/mL | 52.31 (13.88–197.16) | <0.001 | 34.00 | <0.001 | 0.940 (0.889–0.991) | <0.001 |
| Admission HR >120 bpm | 4.56 (1.63–12.75) | 0.004 | 3.47 | <0.001 | 0.613 (0.490–0.736) | <0.001 |
| Prone positioning—No | 3.42 (1.28–9.19) | 0.0146 | | | | |
| Gender—male | 1.49 (0.49–4.43) | 0.6043 | | | | |
| Comorbidity—present | 2.65 (0.92–7.64) | 0.0718 | | | | |

HFNOT, high-flow nasal oxygen therapy; IL-6, interleukin-6; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; ROX index, respiratory rate-oxygenation index; RBS, random blood sugar; AUROC, area under receiver operating characteristic curve; OR, odds ratio; CI, confidence interval




**Figs 3A and B:** ROC curves of (A) Age; APACHE II, SOFA, RBS, IL-6, D-dimer, and HR; (B) ROX index at 1 hour, ROX index at 6 hours, $PaO_2/FiO_2$ ratio (before HFNOT), and $SpO_2$ (before HFNOT) for HFNOT failure

AHRF, showed the gradual and significant impact of HFNOT on oxygenation status ($PaO_2/FiO_2$) over four consecutive time points (i.e.; at 1 hour, 6 hours, 7th day, and 14th day). The majority of our cohort had profound hypoxemia [median (IQR) $PaO_2/FiO_2$ ratio, 99.5 (80–110) mm Hg] at admission to ICU. Even with such a low P/F ratio, HFNOT remarkably outperformed with a success rate of 71%. However, the effect was assessed to be significantly higher in group of the patients who were successfully managed on HFNOT compared to those who failed HFNOT. Significant improvement in $PaO_2/FiO_2$ ratio may be explained by adequate and reliable oxygen

**Table 5:** Various complication of HFNOT

| *Complications* | *All patients (n = 114)* | *HFNOT success (n = 81)* | *HFNOT failure (n = 33)* | *p value*[†] |
|---|---|---|---|---|
| Air hunger, *n* (%) | 18 (15.8) | 5 (6.1) | 13 (39.4) | <0.0001 |
| Epistaxis, *n* (%) | 21 (18.4) | 14 (17.3) | 7 (21.2) | 0.6052 |
| Pressure ulcer at nares, *n* (%) | 10 (8.8) | 10 (12.3) | 0 (0) | 0.0607 |
| Abdominal distension | 4 (3.5) | 4 (49.4) | 0 (0) | 0.3217 |
| Nasal dryness | 4 (3.5) | 3 (3.7) | 1 (3.0) | 1.000 |
| Pneumothorax | 1 (0.9) | 1 (1.2) | 0 (0) | 1.000 |
| None | 55 (48.2) | 45 (55.6) | 10 (30.3) | 0.0023 |

[†]Fisher's exact test

delivery (both concentration flow) meeting the patients' demand, regularly wearing a surgical mask over high flow cannula, self-awake proning, incentive spirometry, and steam inhalation in our cohort. Application of surgical mask over high-flow cannula significantly improves $PaO_2/FiO_2$ from 83 ± 22 to 111 ± 38 ($p$ <0.001).[17]

Eighty-nine percent of patients who were administered remdesivir improved in terms of various outcomes. However, among those who deteriorated on HFNC, 90.9% actually received remdesivir, so there is statistically no significant difference ($p$ = 0.7533). The reason for this is probably the late presentation to COVID ICU by about 3 days (8.3 ± 1.5 vs 4.9 ± 1.4, $p$ <0.001) and higher severity scores in those who presented late.

Profound hypoxemia before HFNOT application recorded in our study is comparable to that reported in two studies conducted in COVID-19 patients.[14,18] In a prospective study conducted in 293 enrolled patients at two tertiary hospitals in Cape Town, South Africa, the median (IQR) $PaO_2/FiO_2$ ratio was 68 (54–92) with more than half of the patients failing to continue on HFNOT.[18] Similarly, in a retrospective study conducted on 105 patients, the median (IQR) $PaO_2/FiO_2$ ratio was 116.0 (102.1–132.0) with a lower HFNOT failure rate of 38%.[14] Our HFNOT failure rate is comparable to previously reported HFNOT failure rates (32–53%).[19,20] Significant predictors of HFNOT failure in our study, which were obtained using multivariate and ROC analysis, were older age (>65 years), higher APACHE II and SOFA scores, lower P/F ratio (<100), higher IL-6 (>40 pg/mL), D-dimer (>2 mg/L) values, and hyperglycemia (RBS >250 mg/dL). We observed ROX score at 6 hours was a better predictor compared to ROX score at 2 hours. Similarly, two recent investigations noted lower ROX score at 6 hours was highly predictive of HFNOT failure.[14,19] A recent meta-analysis has analyzed the performance of the ROX index to detect HFNC failure in COVID-19 patients with AHRF, which showed a high discriminative value to predict HFNC failure.[21]

In our study, about 36% of patients followed proning, the frequency of which was greater in the HFNOT success group. Failure to prone position was found to be a significant predictor of HFNOT failure on univariate analysis (OR 3.42, CI 1.28–9.19; $p$ <0.05). In a series of 20 patients with ARDS treated with HFNC or NIV, improved oxygenation with awake proning was recorded.[22] Similarly, in a pilot study on 50 consecutive COVID-19 patients presenting to ED with $SpO_2$ <93% on supplemental oxygen, 5 minutes of awake proning improved $SpO_2$ from 84 to 94%.[23] Prone positioning (18.2 vs 35%; p, 0.0114), older age at presentation (70.7 ± 10.7 vs 56 ± 13.6; $p$ <0.001), late presentation to COVID ICU by about 3 days (8.3 ± 1.5 vs 4.9 ± 1.4; $p$ <0.001), and higher severity scores in those who presented late were other confounding factors.

HFNOT significantly reduced subjective sensation to dyspnea and improved comfort score in our cohort. Similarly, other studies also reported better dyspnea score and comfort levels with HFNOT when compared to standard oxygen therapy.[24,25] Improved comfort level with HFNOT could be possibly due to improved humidification of the respiratory gas.[25]

After the initial viral phase, some COVID-19 patients develop a hyper-inflammatory phase, which is characterized by cytokine storm and is frequently accompanied by rapid respiratory deterioration leading to pneumonitis. In these patients, high-dose glucocorticoids and/or IV tocilizumab (TCZ) have been the treatment of choice.[26] Dexamethasone decreases mortality in hospitalized COVID-19 patients, according to the recently published randomized evaluation of COVID-19 therapy (RECOVERY) trial.[27] The favorable effect of dexamethasone was most obvious in patients undergoing invasive mechanical ventilation. These preliminary findings imply that drugs that target dysregulated inflammation could be a promising therapeutic option for COVID-19 patients who are critically unwell. While many other retrospective and observational trials using TCZ in severe COVID-19 have shown encouraging results, more research is needed.[28,29] A systematic review and meta-analysis, however, found no evidence that TCZ improves clinical status or reduces the likelihood of ICU admission or mortality.[30] As a result, combining TCZ with glucocorticoids may be beneficial in preventing invasive mechanical ventilation and/or death in patients with severe COVID-19 pneumonia. In this regard, a recent prospective study found that in COVID-19-associated cytokine storm syndrome, a therapeutic strategy consisting of a course of high-dose methylprednisolone, followed by TCZ if needed, can speed up respiratory recovery, lower hospital mortality, and reduce the likelihood of invasive mechanical ventilation.[31] Because glucocorticoids are safe, readily available, and inexpensive, treating with high-dose glucocorticoids as first-line therapy may be more convenient.

The main strengths of the study were its prospective nature and comparatively large sample size. Another strength compared to other studies was that we captured oxygenation data on 7th day and 14th day also, in order to assess long-term effect of HFNOT on oxygenation. Additionally, we have analyzed various predictive variables of HFNOT failure using two different statistical tests: multivariate logistic regression and ROC analysis.

Compared to all previous studies, we recorded higher severity of illness (admission mean APACHE II, 15.1 ± 4.6 and SOFA, 6.5 ± 1.9). In other studies, APACHE II and SOFA scores were in the range between 8–10 and 3–5, respectively.[12,14,19] The probable reasons for higher severity scores could be delayed presentation to our facility and many of them already had spent an average of 6–7 days in other COVID facilities before referral to our centre. This also explains lower levels of baseline hypoxemia and a higher respiratory rate at admission to our facility. The successful group spent a long time in ICU due to profound hypoxemia at baseline and difficult weaning off HFNOT due to probably pulmonary fibrosis or peripheral pulmonary artery embolisms patients may have developed over the course of the disease.

Debate continues on the best modality of respiratory support in severe COVID-19 pneumonia and AHRF. In this regard, HFNOT offers various significant advantages over invasive and other noninvasive devices in terms of higher oxygenation score, decreased risk of

tracheal intubation[32,33] better comfort score and less incidence of nasal and facial skin breakdown, better oral hygiene, speech, higher compliance to device continuation, lesser need of sedative, higher response to awake self-proning (compared to NIV),[24] better comfort level, lower dyspnea score, lesser incidence of hemodynamic collapse, shock, complications such as barotrauma, critical illness polyneuropathy, death (compared to IMV). Noninvasive ventilators necessitate ventilator parameter adjustments and patient tolerance monitoring, which adds to the effort and difficulties for nurses and physicians. HFNC, on the other hand, is more user-friendly. When patients have a high tolerance and cooperate well, a central monitor that analyses changes in HFNC patients' oxygenation and breathing rates minimizes nurses' responsibilities. Most patients tolerate HFNC well, especially when they require long-term oxygen therapy, reducing the likelihood of unwillingness to cooperate or treatment denial due to intolerance. Some HFNC patients opt for enteral feeding, which eliminates the significant risk of infection associated with indwelling nasogastric tubes and also lowers reflux inspiration induced by noninvasive ventilators' gastrointestinal flatulence.[11]

Nevertheless, NIV may be better than HFNOT in improving oxygenation parameters due to higher mean airway pressure, however, at the cost of various complications and intolerance. Moreover, less sick patients (APACHE II <10) with stable hemodynamics requiring HFNOT can be managed in a "high flow ward" with basic monitoring and nursing requirements. That may spare a greater number of ICU beds for sicker COVID-19 patients. In our case, the majority of patients on HFNOT were shifted to a "high-flow ward," after stabilization of respiratory parameters after a week's time, where they were gradually weaned off to SOT and then room air.

The limitations of our study were that being a single-centre study, the results need to be critically interpreted before extrapolating to patients in different geographical locations, with diverse comorbidities and severity scores. Another limitation was that we could not study any radiological variable and also failed to capture data on hospital-acquired infections. Compared to NIV, during HFNOT, better provision of enteral protein-energy delivery was possible due to less incidence of abdominal distension and improved tolerance to HFNOT. This aspect should be tested and explored further in future research. Another factor that needs attention is active mobilization; incentive spirometry practice with HFNOT may have reduced the incidence of critical illness myopathy or polyneuropathy despite various risk factors present (such as prolonged ICU LOS, steroid use, and hyperglycaemia). This aspect should also be a leading point of exploration in future directions.

## Conclusion

In COVID-19 patients with AHRF, the use of HFNOT significantly improved oxygenation level, dyspnea score and comfort level. Age >65 years, SOFA >7, APACHE II >20, admission $PaO_2/FiO_2$ ratio ≤100, $SpO_2$ ≤70%, HR >120 bpm, D-dimer >2 mg/L, IL-6 >40 pg/mL, RBS >250 mg/dL, 6 hours ROX score ≤3.5, and 1 hour ROX score ≤3 were independent prognostic factors of HFNOT failure. We strongly recommend selecting HFNOT as an initial respiratory support device to manage acute hypoxemic respiratory failure in COVID-19, due to its effectiveness, safety, and ease of application with minimal training and minimal monitoring and nursing requirement.

## Orcid

*Mohd Saif Khan* https://orcid.org/0000-0002-9430-0076
*Jay Prakash* https://orcid.org/0000-0002-5290-3848
*Sudipto Banerjee* https://orcid.org/0000-0003-3010-5041
*Pradip K Bhattacharya* https://orcid.org/0000-0002-0219-385X
*Raman Kumar* https://orcid.org/0000-0002-1220-4137
*Deepak K Nirala* https://orcid.org/0000-0003-1348-828X

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