High-Flow Nasal Cannula Treatment in Patients with COVID-19 Acute Hypoxemic Respiratory Failure

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Abstract

Background

The increasing burden of coronavirus disease 2019 (COVID-19)-related acute hypoxemic respiratory failure (AHRF) is straining intensive care unit (ICU) resources globally. Early use of high-flow nasal cannula (HFNC) decreases the need for endotracheal intubation (EI) in different causes of respiratory failure. While HFNC is used in COVID-19-related AHRF, its efficacy remains to be investigated. We aimed to examine whether the use of high-flow nasal oxygen therapy (HFNO) prevents the need for intubation in COVID-19 with (AHRF).

Methods

This is a single-center prospective observational study that was conducted at a tertiary teaching hospital in Saudi Arabia the period from April, 2020 to August, 2020. Adults patients admitted to the ICU with AHRF secondary to COVID-19 pneumonia and managed with HFNC were included. We excluded hemodynamically unstable patients and those who were intubated or managed with non-invasive ventilation. Patients' data and clinical outcomes were pre-defined. The primary outcome was to determine the rate of EI among patients who were treated with HFNC. Secondary outcomes included predictors of HFNC success/failure, mortality, and hospital length of stay.

Results

We consecutively screened 111 hospitalized COVID-19 patients with AHRF,. Out of those, 44 (40%) patients received HFNC with a median duration of three days (IQR, 1–5). The median age was 57 years (interquartile range [IQR], 46–64), and 82% were men. HFNC failure and EI occurred in 29 (66%) patients. Patients who failed HFNC treatment had higher risk of death compared to those who did not (52% vs. 0%; $p=0.001$). At baseline, the prevalence of hypertension, chronic kidney disease, and asthma was higher in the HFNC failure group. After adjustment for possible confounders, a high Sequential Organ Failure Assessment (SOFA) score and a low ROX index were significantly associated with HFNC failure (hazard ratio [HR], 1.42; 95% confidence interval [CI], 1.04–1.93; $p=0.025$; and HR, 0.61; 95% CI, 0.42–0.88; $p=0.008$, respectively).

Conclusions

In this prospective study, one-third of hypoxemic COVID-19 patients who received HFNC did not require intubation. High SOFA score and low ROX index were associated with HFNC failure.

Key Messages

- We evaluated the rate of EI due to persisting or worsening hypoxemia after the application of HFNC.
- Third (15 patients) of COVID-19 patients with AHRF who were managed with HFNC did not require EI and they were discharged uneventfully.

- High SOFA score and low ROX index were significantly associated with failure of HFNC therapy.
- Mortality was significantly associated with HFNC treatment failure; therefore, early prediction of HFNC failure and continuous monitoring is vital.

Background

High-flow nasal cannula (HFNC) is a non-invasive method that delivers a high flow of oxygenated, heated, and humidified gas. In the last few years, HFNC has been effective in the management of critically ill patients with acute respiratory failure, showing better outcomes at 90 days than conventional oxygen therapy and non-invasive ventilation (NIV) [1–3]. The burden of COVID-19-related respiratory failure is exerting a strain on the intensive care unit (ICU) resources worldwide, including shortage of ventilators [4]. Thus, an alternative to invasive ventilation may be of substantial benefit.

The risks and benefits of HFNC must also be well understood as recent guidelines did not recommend the use of NIV for *de novo* hypoxemic respiratory failure or pandemic-related viral illness [5].

HFNC has been increasingly used to avoid endotracheal intubation (EI) in patients with acute hypoxemic respiratory failure (AHRF) in recent years [6]; however, its use has rarely been reported in patients with severe acute respiratory infection [7]. Frat et al.[1] found that compared with standard oxygen therapy and NIV, HFNC can effectively reduce the rate of EI in patients with AHRF mainly caused by community-associated pneumonia, given its favorable physiological effects, including low-level of positive end-expiratory pressure (PEEP) to keep the alveoli open, washout of nasopharyngeal dead space to improve ventilation efficiency, improved breathing pattern, and enhanced airway heating and humidification function [8, 9]. Figure 1 illustrates the physiological benefits during HFNC treatment.

During the early surge of COVID-19, emergent intubation practices were advised to decrease the risk of aerosol-generating procedures and meet the rising oxygen requirement and decline in respiratory status [10]. However, studies have reported high mortality rates with the invasive ventilation methods in patients with COVID-19-related AHRF [11, 12].

Few observational studies have shown the advantage of HFNC in avoiding EI and reversing hypoxemia in patients with COVID-19-related AHRF [13–16]. Nevertheless, conclusive evidence is still limited, and the role of HFNC remains controversial in the management of COVID-19-related AHRF. Data on the efficacy of HFNC in this population are scarce, including data for identifying patients who might benefit from HFNC, predictors of HFNC failure, and clinical outcomes. Therefore, this study aimed to investigate the effectiveness of HFNC in reducing the need for EI in critically ill patients with COVID-19-related AHRF and identify factors that can predict the success or failure of HFNC use.

Methods

Objectives

The aims of this study are: 1) to determine the incidence of endotracheal intubation among adults with COVID-19 and AHRF receiving HFNC; 2) to determine clinical variables associated with HFNC failure in this population.

Study Design and Settings

This is a single-center, prospective observational study that was conducted in the ICU at King Fahad Hospital of the University, Kingdom of Saudi Arabia from April 1, 2020, to August 1, 2020. The study followed the ethical standards of the institutional and national research committees and with the amended Helsinki Declaration (as revised in 2013). Ethical approval for this study was obtained from the institutional review board of Imam Abdulrahman Bin Faisal University, Kingdom of Saudi Arabia. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines.

Participants

Consecutively, all ICU patients who were diagnosed with COVID-19-related AHRF defined by oxygen saturation (SpO_2) of $<92\%$ despite conventional supplemental oxygen and then managed with HFNC were screened. The diagnosis of Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) infection was made by real-time reverse transcription-polymerase chain reaction (RT-PCR).

We excluded hemodynamically unstable patients, patients intubated before HFNC application, those requiring intubation as per the treating physician, patients receiving non-invasive ventilation, patients with “Do Not Resuscitate” orders.

Study Procedure

The primary treating team made all treatment decisions with no direct or indirect influence from the research team. Patient management was based on both the recommendations issued by the Saudi Critical Care Society and Survival Sepsis Campaign clinical practice guidelines for the management of critically ill COVID-19 patients [17, 18].

All patients with $\text{SpO}_2 <90\%$ were started on supplemental oxygen therapy. The SpO_2 target of oxygen therapy was $92\%–96\%$. Those who did not achieve the targeted saturation despite conventional oxygen supply were started on HFNC or Non-invasive ventilation (NIV), as tolerated. We followed only patients who underwent HFNC therapy. Patients were closely monitored by the medical staff for early detection of respiratory deterioration and the need for EI. The flow of HFNC was started from low levels and titrated gradually to the range of $30–60 \text{ L/min}$, as tolerated by the patient. The fraction of inspired oxygen (FiO_2) was set to maintain the SpO_2 between 92% and 96% . To ensure the safety of the treating personnel, several measures were taken to decrease aerosol transmission, including admission to negative pressure rooms as available, use of high-efficiency particulate air filters, use of personal protective equipment for all patient encounters, and avoiding aerosol-generating procedures. HFNC failure was defined as the

failure to adequately maintain targeted SpO₂, clinical or laboratory indication of respiratory fatigue, and the need for EI.

Data Collection

Data were collected using pre-designed case report forms that were filled for all patients prospectively. Data were extracted by two of the authors and reviewed by a third independent author. We collected data on demographics, comorbidities, ICU admission, vital signs, arterial blood gases, mode of oxygen therapy at the time of gas sampling, Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II). Furthermore, the PaO₂/FiO₂ ratio was calculated at ICU admission. We recorded the duration and flow of HFNC, FiO₂, and SpO₂ at several intervals. Prone position duration and intubation rate were also recorded. The Respiratory rate-Oxygenation (ROX) index (ratio of SpO₂/FiO₂ to respiratory rate [RR]) was calculated prior to starting HFNC and at 2, 6, 12, 18, and 24 hours after HFNC application. The 30-day outcome variables (intubation, hospital and ICU length of stay [LOS], and in-hospital mortality) were also collected.

Outcome Measures

The primary outcome was to determine the rate of EI due to persisting or worsening hypoxemia after the application of HFNC (i.e. HFNC failure). The secondary outcomes included predictors of HFNC success/failure, in-hospital mortality rate, ICU and hospital LOS.

Statistical Analysis

Statistical analysis was conducted using the IBM Statistical Package for Social Sciences (SPSS) version 22.2 (IBM, Armonk, NY, USA). Descriptive analysis was performed, and variables were presented as mean and standard deviation (SD) or median with inter-quartile range (IQR) as appropriate, while categorical variables were expressed as numbers and percentages. Normality of the data was determined using Shapiro-Wilk test and p-values greater than 0.05 suggested that data is following normal distribution. Therefore, basing on normality test results student's t-test and the median test were used for continuous variables and chi-square and Fisher's exact test, for percentages as appropriate, according to the distribution of the data. In the present study, we used the established ROX index cutoff value of 4.88 at different time points (2, 6, and 12 hours) from a previous study [19]. Respiratory variables at different points (prior to HFNC, 2, 6, 12, 18 hours after HFNC) were assessed by the area under the receiver operating characteristic curve (AUROC) for measuring the accuracy of different respiratory variables at different time points in discriminating patients who most likely will experience HFNC failure.

Kaplan-Meier curves were used to determine the probability of intubation for patients with below and above ROX cutoff point and to determine the probability of intubation in hypoxemic COVID-19 patients receiving HFNC versus patients receiving usual acute respiratory distress syndrome care. Log-rank tests were used to compare these curves. Cox-proportional regression analysis was used to evaluate the hazard ratio (HR) for the cumulative probability of HFNC treatment failure based on the duration of HFNC

treatment. Univariate analysis of all variables was performed to assess the factors associated with the failure of HFNC treatment; variables with a p-value less than 0.1 were retained and included in the multivariate Cox regression model. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 111 ICU patients with confirmed COVID-19 were screened for eligibility. The median age was 57 years (IQR, 46–64 years) and 20 (18%) were females. Table 1 shows the demographic characteristics of patients upon admission to the hospital and the ICU. The treating team initiated HFNC treatment in 44 patients (40%) after admission to the ICU. The median duration of HFNC was 3 days (IQR, 1–5 days), with a median flow of 60 L/min (IQR, 42–60 L/min) and a 95% FiO₂ (IQR, 80–100%).

Table 1

Demographic, comorbidities, and vital signs characteristics of patients upon admission.

Variables	Total cohort n = 101
Demographic information:	
Age, median (IQR)	57 (46–64) years
Sex:	
Male, n (%)	91 (82%)
Female, n (%)	20 (18%)
Smoking:	
Yes, n (%)	6 (5%)
No, n (%)	33 (30%)
Unknown, n (%)	72 (65%)
Comorbidities:	
Diabetes, n (%)	58 (52%)
Hypertension, n (%)	47 (42%)
Ischemic heart disease, n (%)	7 (6%)
Chronic lung disease, n (%)	1 (1%)
COPD, n (%)	0 (0%)
Bronchial asthma, n (%)	8 (7%)
Chronic liver disease, n (%)	2 (2%)
Chronic kidney disease, n (%)	13 (12%)
Immunocompromised status, n (%)	4 (4%)
Vital signs on ICU admission:	
Systolic blood pressure, median (IQR)	124 (110–139) mm Hg
Diastolic blood pressure, median (IQR)	73 (64–83) mm Hg
Heart rate, median (IQR)	97 (84–111) beats/minute
Respiratory rate, median (IQR)	29 (24–38) breaths/minute
Oxygen saturation, median (IQR)	95 (90–96) %
IQR, interquartile; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.	

Twenty-nine (66%) patients experienced HFNC failure and required EI. The median duration from initiation of HFNC treatment to EI was 2 days (IQR, 1–7 days). The baseline information upon ICU admission in a comparison between HFNC success and failure groups is presented in Table 2. Besides, the cohort of patients that failed HFNC therapy had a higher proportion of comorbidities (i.e. hypertension, chronic kidney disease, and asthma). The PaO₂/ FiO₂ ratio was higher in cases of HFNC success than in cases of failure (p = 0.001).

Table 2
Baseline information of patients upon ICU admission.

Variables		HFNC Success (n = 15)	HFNC Failure (n = 29)	P-value
Demographics	Age, mean ± SD	50.67 ± 12.92 years	60.21 ± 13.47 years	0.029*
	Male, n (%)	13 (87%)	25 (86%)	0.673
	Female, n (%)	2 (13%)	4 (14%)	
Commodities	Chronic Lung Disease, n (%)	1 (7%)	0 (0%)	0.341
	Bronchial Asthma, n (%)	1 (7%)	4 (14%)	0.437
	Chronic Kidney Disease, n (%)	1 (7%)	4 (14%)	0.437
	Immunocompromised Status, n (%)	1 (7%)	0 (0%)	0.341
	Hypertension, n (%)	7 (47%)	15 (52%)	0.5
	Ischemic Heart Disease, n (%)	1 (7%)	2 (7%)	0.736
Respiratory Variables	ROX Score, mean ± SD	5.16 ± 2.2	4.06 ± 1.49	0.055
	APPACHE-II Score, mean ± SD	7.6 ± 4.39	13.41 ± 6.91	0.005*
	SOFA Score, mean ± SD	3 ± 1.51	4.45 ± 2.11	0.023*
	PaO ₂ /FiO ₂ ratio, mean ± SD	96.07 ± 67.04, mmHg	43.31 ± 35.11, mmHg	0.001*
	Respiratory Rate, mean ± SD	27.8 ± 6.44	32.1 ± 6.46	0.042*

***Significant at 0.05 level of significance**

HFNC, high-flow nasal cannula; SD, standard deviation; ROX, Respiratory rate-Oxygenation; APPACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; PaO₂/FiO₂, arterial partial pressure of oxygen/fraction of inspired oxygen.

The median ROX score calculated before treatment initiation was higher in cases of HFNC success (4.98; IQR, 3.94–7.8) than HFNC failure (3.69; IQR, 2.96–4.96), but the difference was not statistically significant ($p = 0.08$). Higher APACHE-II score, SOFA score, and RR were significantly associated with the failure of HFNC therapy ($p = 0.005$, $p = 0.023$, and $p = 0.042$, respectively). The median duration of HFNC treatment was shorter in successful HFNC cases (3 days; IQR, 1–5 days) than in failed HFNC cases (6 days; IQR, 4–7.5 days) ($p = 0.002$).

Mortality was significantly associated with HFNC treatment failure and a longer ICU LOS. Table 3 presents the clinical outcomes of the patients treated with HFNC. Oxygen saturation at the initiation of HFNC was high in the success group (median 96%; IQR, 95–97%). Respiratory variables' measurements during HFNC treatment are presented in Table 4. The RR was lower after 24 hours of HFNC initiation in the success group at a median of 21 breaths/min (IQR, 20–24 breaths/min). There were no significant differences in the FiO_2 values between successful and failed cases. The ROX score improved after 6 hours of HFNC initiation in the success group compared to the failure group.

Table 3
Outcomes of patients with COVID-19 AHRF receiving HFNC treatment.

Outcomes	HFNC success (n = 15)	HFNC failure (n = 29)	P-value
Death, n (%)	0 (0%)	15 (52%)	0.001
Discharged or still in ICU, n (%)	15 (100%)	14 (48%)	
ICU LOS, median (IQR)	6 (6–11) days	11 (6–17) days	0.043
Hospital LOS, median (IQR)	17 (14–26) days	14 (8–20) days	0.477
ICU, Intensive Care Unit; LOS, Length of Stay; IQR, Interquartile Range.			

Table 4
The effect of respiratory variables during HFNC treatment.

Variables	Measurement Time	HFNC success (n = 15)	HFNC failure (n = 29)	P-value
SpO ₂	Prior to HFNC, median (IQR)	96 (95–97) %	92 (90–96)	0.005*
	2 hours, median (IQR)	96 (94–97) %	93 (90–96) %	0.194
	6 hours, median (IQR)	95 (91–96) %	94 (90–96) %	0.969
	12 hours, median (IQR)	95 (93–97) %	93 (90–96) %	0.236
	18 hours, median (IQR)	95 (93–98) %	95 (90–97) %	0.07
	24 hours, median (IQR)	96 (95–96) %	94 (90–98) %	0.680
RR	Prior to HFNC, median (IQR)	23 (20–27) bpm	30 (23–36) bpm	0.048*
	2 hours, median (IQR)	25 (20–32) bpm	27 (23–32) bpm	0.794
	6 hours, median (IQR)	25 (22–28) bpm	25 (20–31) bpm	1.00
	12 hours, median (IQR)	24 (21–29) bpm	27 (22–30) bpm	0.245
	18 hours, median (IQR)	24 (23–27) bpm	26 (22–33) bpm	0.214
	24 hours, median (IQR)	21 (20–24) bpm	25 (20–30) bpm	0.036*
FiO ₂	Prior to HFNC, median (IQR)	75 (60–100) %	90 (60–100) %	0.198
	2 hours, median (IQR)	75 (60–100) %	90 (80–100) %	0.303
	6 hours, median (IQR)	75 (60–95) %	95 (80–100) %	0.209
	12 hours, median (IQR)	70 (60–90) %	95 (80–100) %	0.173
	18 hours, median (IQR)	75 (60–100) %	90 (70–100) %	0.140
	24 hours, median (IQR)	70 (60–100) %	90 (70–100) %	0.140
ROX	Prior to HFNC, median (IQR)	4.98 (3.94–7.8)	3.69 (2.96–4.96)	0.078
	2 hours, median (IQR)	4.95 (3.29–8.0)	4.02 (3.46–5.11)	0.143
	6 hours, median (IQR)	5.05 (4.25–5.8)	4.09 (3.16–6.1)	0.245
	12 hours, median (IQR)	5.80 (5.18–6.28)	3.53 (3.14–5.0)	0.021*

***Significant at 0.05 level of significance**

HFNC, high-flow nasal cannula; IQR, interquartile; SpO₂, oxygen saturation; RR, respiratory rate; bpm, breaths per minute; FiO₂, fraction of inspired oxygen; ROX, Respiratory rate-Oxygenation.

Variables	Measurement Time	HFNC success (n = 15)	HFNC failure (n = 29)	P-value
	18 hours, median (IQR)	4.94 (4.01–6.4)	3.60 (2.86–6.3)	0.685
	24 hours, median (IQR)	6.05 (4.56–7.1)	4.7 (2.86–6.4)	0.408
*Significant at 0.05 level of significance				
HFNC, high-flow nasal cannula; IQR, interquartile; SpO ₂ , oxygen saturation; RR, respiratory rate; bpm, breaths per minute; FiO ₂ , fraction of inspired oxygen; ROX, Respiratory rate-Oxygenation.				

Table 5

Accuracy of different respiratory variables at different time points for prediction of HFNC Success.

Variables	Measurement Time	AUROC (95% CI)	P-value
SpO ₂	Prior to HFNC	0.619 (0.383–0.855)	0.336
	2 hours	0.638 (0.409–0.868)	0.264
	6 hours	0.481 (0.239–0.722)	0.877
	12 hours	0.646 (0.416–0.876)	0.239
	18 hours	0.569 (0.329–0.809)	0.577
	24 hours	0.581 (0.324–0.838)	0.515
RR	Prior to HFNC	0.208 (0.011–0.404)	0.018*
	2 hours	0.423 (0.174–0.672)	0.535
	6 hours	0.4 (0.163–0.637)	0.42
	12 hours	0.392 (0.156–0.629)	0.385
	18 hours	0.381 (0.147–0.615)	0.336
	24 hours	0.304 (0.079–0.528)	0.114
FiO ₂	Prior to HFNC	0.351 (0.163–0.538)	0.132
	2 hours	0.357 (0.168–0.547)	0.149
	6 hours	0.351 (0.166–0.536)	0.132
	12 hours	0.33 (0.146–0.514)	0.086
	18 hours	0.39 (0.198–0.583)	0.268
	24 hours	0.367 (0.175–0.559)	0.178
ROX	Prior to HFNC	0.792 (0.596–0.988)	0.021*
	2 hours	0.646 (0.399–0.892)	0.249
	6 hours	0.633 (0.389–0.878)	0.291
	12 hours	0.746 (0.523–0.969)	0.052
	18 hours	0.608 (0.364–0.852)	0.391
	24 hours	0.613 (0.371–0.854)	0.373

*Significant at 0.05 level of significance

AUROC, Area Under the Receiver Operating Characteristic curve; CI, confidence interval; HFNC, high-flow nasal cannula; SpO₂, oxygen saturation; RR, respiratory rate; FiO₂, fraction of inspired oxygen; ROX, Respiratory rate-Oxygenation.

The Kaplan-Meier plot for the probability of being free from intubation shows that the risk of intubation was higher among the patients who received usual care than those who received HFNC treatment (Fig. 2). The AUROC of the ROX index for predicting success at the initiation of HFNC treatment was of 0.79 (CI, 0.60–0.99), 0.75 (CI, 0.52–0.97) after 12 hours of therapy, and 0.61 (CI, 0.37–0.85) at 24 hours. The AUROC for SpO₂ after 2 hours of HFNC initiation was 0.64 (CI, 0.41–0.87) and 0.646 (CI, 0.42–0.88) at 12 hours. On the other hand, the RR and FiO₂ did not show good predictive capacity for HFNC failure (Table 4).

Kaplan-Meier plots showed significant differences in the probability of HFNC therapy success, with the cutoff of 4.88 at 2, 6, 12, and 18 hours (Fig. 3A, 3B, 3C, and 3D). The ROX score at 2 hours showed that patients with a score ≥ 4.88 were at a lower risk of EI. A similar probability can be observed at 6, 12, and 18 hours in the plots.

The univariate Cox-regression analysis showed an association between age, APACHE-II, SOFA scores and HFNC failure. After adjustment for possible confounders (sex, RR, cardiac disease, lung disease, PaO₂/FiO₂ ratio, and prone position), a high SOFA score and a low ROX index significantly predicted the failure of HFNC use (Table 6).

Table 6
Cox proportional regression analysis for the prediction of HFNC failure.

Univariate Analysis			Multivariate Analysis	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.02 (0.993–1.051)	0.1*	1.02 (0.975–1.058)	0.456
PaO ₂ /FaO ₂	0.99 (0.984-1)	0.041*	0.99 (0.982–1.004)	0.192
ROX Index ≥ 4.88	0.80 (0.625–1.018)	0.069*	0.61 (0.423–0.877)	0.008**
APACHE-II	1.06 (1.007–1.119)	0.025*	0.98 (0.901–1.067)	0.648
SOFA	1.19 (1.002–1.42)	0.047*	1.42 (1.044–1.926)	0.025**
O ₂ saturation	0.94 (0.877–1.005)	0.071*	0.97 (0.895–1.055)	0.495
*Significant at 0.10 level of significance				
**Significant at 0.05 level of significance				
HR, Hazard Ratio; CI, confidence interval; PaO ₂ /FiO ₂ , arterial partial pressure of oxygen/fraction of inspired oxygen; ROX, Respiratory rate-Oxygenation; APPACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.				

Discussion

In this retrospective observational study of a prospectively collected 44 patients with AHRF from COVID-19, we found that 66% of patients receiving HFNC required EI. Moreover, we found that high SOFA and low ROX index were associated with HFNC failure.

Very few observational studies have looked at HFNC use in COVID-19 patients. Retrospective observational studies report a HFNC failure rate to range between 32–72% [13–16, 20]. The high variability in the reported HFNC failure rates might be attributed to several possible explanations. For instance, the definition of failure was not standardized in all studies, some defined failure as the need for NIV or EI [7, 8], while others defined failure as the need for EI or death [16, 20]. Furthermore, the threshold for intubation varies among ICU physicians as there is no consensus on how to determine HFNC or NIV failure. In addition, hypoxemia, disease intensity, and other baseline characteristics of patients varied between the studies.

Our observational study confirmed the observation of previous studies, where mortality was found to be higher in cases of HFNC treatment failure than in cases of success (34% versus 0%). Thus, clinicians treating hypoxemic COVID-19 patients should identify patients who are likely to benefit from HFNC treatment. Roca et al. found that the ROX index predicts HFNC failure in patients with AHRF secondary to pneumonia [19]. They reported that a ROX of ≥ 4.88 measured after HFNC therapy at 2, 6, and 12 hours was associated with a lower risk of HFNC failure [19]. However, the ROX index has not yet been validated in hypoxemic COVID-19 patients. In our study, we measured the ROX index prior to HFNC and at 2, 6, 12, 18, and 24 hours after HFNC treatment. The results showed a significant difference in the probability of success with the cutoff of 4.88 at 2, 6, 12, and 18 hours. After adjustment for other confounders, the ROX index and SOFA score were still strong predictors of HFNC treatment failure. In terms of the baseline characteristics upon ICU admission, the prevalence of hypertension, chronic kidney disease, and asthma was higher in patients with HFNC failure. However, the $\text{PaO}_2/\text{FiO}_2$ ratio at baseline was found to be higher in successful HFNC cases than in failed HFNC cases.

Similarly, another study included 62 patients with COVID-19-related AHRF, which showed that a ROX index measured after 4 hours of HFNC was significantly associated with HFNC success and low risk of EI [20]. Our study adds to the existing knowledge by showing the potential utility of the previously established cutoff of ROX index for monitoring HFNC treatment in COVID-19-related AHRF. Another study showed that $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg at ICU admission was a significant predictor of HFNC failure [13]. The study by Wang et al.¹⁴ showed that none of the patients with $\text{PaO}_2/\text{FiO}_2 > 200$ mm Hg had HFNC failure compared to 63% failure in patients with low $\text{PaO}_2/\text{FiO}_2 (\leq 200$ mm Hg). Additionally, the RR was found to decrease significantly after 1–2 hours of HFNC in the successful cases [13].

Another retrospective study of 109 patients who were treated with HFNC, found that chronic obstructive pulmonary disease, high SOFA score at ICU admission, and high white blood cell count were predictors of HFNC failure [15]. Interestingly, after adjusting for possible confounding variables, longer duration from ICU admission to EI was not associated with increased mortality in their cohort. A multicenter retrospective study included 43 patients treated with HFNC reported success with HFNC in 53.5% of the

patients, while 46.5% needed EI or died [16]. While the overall hospital mortality of that cohort was 32.9%, the hospital mortality rate for failed HFNC was 65%. Male sex and low SpO₂ at admission were independent predictors of HFNC failure in the multivariate regression model [16]. The accuracy of multiple monitoring parameters in predicting HFNC failure in COVID-19-related AHRF was assessed in one study, where RR $\geq$ 26/min after half an hour of HFNC application was associated with a higher risk of HFNC failure. However, the study was limited by small sample size (32 patients) and high SpO₂ (100%) observed in a third of their cohort, which could participate in decreasing the contribution of SpO₂/FiO₂ in the diagnostic accuracy of ROX [21].

Ferrando et al. have examined the use of HFNC with awake prone positioning versus HFNC alone, in which they reported that out of the entire cohort, 82 patients (41%) required EI [22]. They observed that awake prone positioning combined with HFNC did not reduce the EI rate compared to HFNC alone, with no significant difference in neither ICU LOS nor 28-day mortality rate [22]. Nevertheless, these findings need to be confirmed with the currently ongoing multiple randomized controlled trials. Although this study has shown that awake prone positioning does not affect intubation and mortality rates, HFNC may remain an effective modality of respiratory support in which 117 patients (59%) of 199 patients on HFNC did not require EI and mechanical ventilation.

Most recently, a prospective multicenter study that involved 293 patients has reported 53% HFNC failure rate, in which half of the patients did not require mechanical ventilation [23]. Moreover, they found that a high ROX index (per point increase) at 6 hours to be significantly associated with HFNC success cases (adjusted HR, 0.42; 95% CI [0.33–0.54]; $p < 0.001$). However, the mortality in patients who failed HFNC treatment was very high (92%) [23]. This considerably high rate is inconsistent with neither previous studies nor the current study findings, which might be attributed to several reasons, including resource-constrained setting, the majority (64%) of their cohort were admitted to the ward in a non-critical care environment, and limited access to ICU expertise [23]. Besides, there was a significant difference between the admitting settings of the two groups, where 45% of successfully treated patients were admitted to ICU setting compared to only 28% of the failed HFNC cases were treated in ICU setting ($p = 0.004$) [23]. Although this study adds a great value to the current literature, it was aimed to assess the impact of HFNC in a resource-constrained setting; thus, it does not reflect the actual rate of HFNC failure mortality in an ICU care setting with optimal monitoring.

These findings indicate that with the application of appropriate selection criteria, a significant number of patients with COVID-19-related AHRF could avoid EI. Yet, HFNC therapy should not be provided to patients at a high risk of failure due to increased mortality in this particular group of patients.

This study has several strengths. First, it is one of the very few studies that investigated the use of HFNC in AHRF due to COVID-19, which can be a useful and safe intervention for appropriately selected patients in a pandemic situation. In addition, consecutive sampling, duplicate data collection, and quality monitoring are important strengthening points. The study looked at many different possible predictors of success and failure of HFNC treatment that can help physicians and respiratory therapists to select

patients with the best chance of success and not delay EI when necessary. Another strengthening point is the adherence of the treating team with guidelines issued by the Saudi Critical Care Society and Survival Sepsis Campaign, in which there was no major changes or variations in patients management throughout the study period [17, 18].

However, this study also has several limitations. The observational nature of the study, lack of a control arm, plus a small sample size are important limiting factors in terms of clinical outcomes. Furthermore, since this was a single-center study, the generalizability of the results is limited. Further prospective randomized studies with a controlled arm are needed to confirm the results of this study.

Conclusions

This study has demonstrated that HFNC might be an effective and safe method for improving oxygenation in mild forms of AHRF secondary to COVID-19 who are not responding to conventional oxygen therapy. One-third of the hospitalized COVID-19 patients who received HFNC did not require intubation. However, the failure of HFNC was associated with a higher in-hospital mortality rate. Therefore, close monitoring and early prediction of HFNC failure should be warranted. Our study found that patients with a low ROX index and/or a high SOFA score were more likely to experience HFNC failure.

List Of Abbreviations

AHRF, Acute Hypoxemic Respiratory Failure; APACHE II, Acute Physiology and Chronic Health Evaluation II; AUROC, Area Under the Receiver Operating Characteristic curve; CI, Confidence Interval; COVID-19, Coronavirus Disease; EI, Endotracheal Intubation; FiO₂, Fraction of inspired Oxygen; HFNC, High-Flow Nasal Cannula; HR, Hazard Ratio; ICU, Intensive Care Unit; IQR, Interquartile Range; LOS, Length of Stay; NIV, Non-invasive Ventilation; RR, Respiratory Rate; SARS-CoV-2, Severe Acute Respiratory Syndrome Corona Virus-2; SD, Standard Deviation; SOFA, Sequential Organ Failure Assessment; SpO₂, Oxygen Saturation.

Declarations

Ethical approval:

The monitoring office for research & research ethics (MORRE) at Imam Abdulrahman Bin Faisal University (IAU) has granted this study with ethical permission (IRB-2020-610-Med). The confidentiality of patients was maintained throughout the study conduction and reporting.

Data availability statement:

All de-identified data used and/or analysed in this study are available from the corresponding author upon reasonable request.

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Figures

Figure 1

illustration of the physiological benefits of the use of High Flow Nasal Cannula (HFNC). “Illustration by Mesa Schumacher.” All rights reserved.

Figure 2

Kaplan-Meier plot showing the intubation probability between patients who were on High-Flow Nasal Cannula (HFNC) versus patients on usual care.

Figure 3

Kaplan-Meier plots demonstrating HFNC success probability stratified at different time intervals; A, ROX score at 2 hours; B, ROX score at 6 hours; C, ROX score at 12 hours; D, ROX score at 18 hours.

Supplementary Files

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- [STROBEChecklistHighflowNasalCannulaTreatment.docx](#)