Original Article

High-Flow Nasal Cannula Treatment in Patients with COVID-19 Acute Hypoxemic Respiratory Failure: A Prospective Cohort Study

Mohammed S Alshahrani[1,2], Hassan M. Alshaqaq[3], Jehan Alhumaid[4], Ammar A. Binammar[3], Khalid H AlSalem[1], Abdulazez Alghamdi[5], Ahmed Abdulhady[6], Moamen Yehia[7], Amal AlSulaibikh[1], Mohammed Al Jumaan[1], Waleed H Albuli[8], Talal Ibrahim[2], Abdullah A. Yousef[8], Yousef Almubarak[2], Waleed Alhazzani[9,10]

Departments of [1]Emergency Medicine, [2]Intensive Care and [8]Pediatrics, King Fahd Hospital of the University, College of Medicine, [3]College of Medicine, [4]Preventive Dental Sciences Department, College of Dentistry, [5]Respiratory Care Services, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Kingdom of Saudi Arabia, [6]Critical Care Department, Faculty of Medicine, Alexandria University, [7]Critical Care Department, Faculty of Medicine, Cairo University, Egypt, Departments of [9]Medicine and [10]Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

Abstract

Background: Early use of high-flow nasal cannula (HFNC) decreases the need for endotracheal intubation (EI) in different respiratory failure causes. While HFNC is used in coronavirus disease 2019 (COVID-19)-related acute hypoxemic respiratory failure (AHRF) under weak recommendations, its efficacy remains to be investigated.

Objectives: The primary objective was to examine HFNC efficacy in preventing EI among COVID-19 patients with AHRF. Secondary objectives were to determine predictors of HFNC success/failure, mortality rate, and length of hospital and intensive care unit (ICU) stay.

Patients and Methods: This is a prospective cohort study conducted at a single tertiary care centre in Saudi Arabia from April to August 2020. Adult patients admitted to the ICU with AHRF secondary to COVID-19 pneumonia and managed with HFNC were included. We excluded patients who were intubated or managed with non-invasive ventilation before HFNC.

Results: Forty-four patients received HFNC for a median duration of 3 days (interquartile range, 1–5 days). The mean age was 57 ± 14 years, and 86% were men. HFNC failure and EI occurred in 29 (66%) patients. Patients in whom HNFC treatment failed had a higher risk of death (52% versus 0%; $P = 0.001$). After adjusting for confounding factors, a high 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: 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.

Keywords: Acute hypoxemic respiratory failure, COVID-19, endotracheal intubation, high-flow nasal cannula, oxygen therapy, SARS-CoV-2

Address for correspondence: Dr. Mohammed S Alshahrani, Departments of Emergency Medicine and Intensive Care, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, P.O. Box: 40236, Dammam, 31952, Saudi Arabia.
E-mail: msshahrani@iau.edu.sa

Submitted: 28-May-2021 **Revised:** 03-Aug-2021 **Accepted:** 05-Aug-2021 **Published:** 31-Aug-2021

Access this article online	
Quick Response Code:	Website: www.sjmms.net
	DOI: 10.4103/sjmms.sjmms_316_21

How to cite this article: Alshahrani MS, Alshaqaq HM, Alhumaid J, Binammar AA, AlSalem KH, Alghamdi A, *et al*. High-Flow nasal cannula treatment in patients with COVID-19 acute hypoxemic respiratory failure: A prospective cohort study. Saudi J Med Med Sci 2021;9:215-22.

INTRODUCTION

High-flow nasal cannula (HFNC) is a non-invasive method that delivers a high flow of oxygenated, heated and humidified gas. In the past few years, HFNC has been used to effectively manage critically ill patients with acute respiratory failure, with better outcomes at 90 days than conventional oxygen therapy and non-invasive ventilation (NIV).[1-3]

Specifically, in patients with acute hypoxemic respiratory failure (AHRF), HFNC has been increasingly used to avoid endotracheal intubation (EI);[4] however, its use has rarely been reported in cases with severe acute respiratory infection.[5] 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 favourable physiological effects, including low-level of positive end-expiratory pressure (PEEP), washout of nasopharyngeal dead space, improved breathing pattern, and enhanced airway heating and humidification.[6,7] Figure 1 illustrates the physiological benefits during HFNC treatment.

The burden of respiratory failure secondary to COVID-19 has exerted a strain on the intensive care unit (ICU) resources worldwide, including a shortage of ventilators.[8] During the early phase 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.[9] However, studies have reported high mortality rates to be associated with invasive ventilation in COVID-19-related AHRF.[10,11] Thus, an alternative to invasive ventilation may be of substantial benefit.

The risks and benefits of HFNC must be well understood, as the 2017 ERS/ATS clinical practice guidelines did not recommend the use of NIV for de novo hypoxemic respiratory failure or pandemic-related viral illness.[12] Nonetheless, few observational studies have shown the advantage of HFNC in avoiding EI and reversing hypoxemia in patients with COVID-19-related AHRF.[13-16] However, conclusive evidence regarding the efficacy of HFNC in the management of COVID-19-related AHRF is limited. Therefore, there is need for further studies to determine predictors of HNFC success and failure as well as assess the clinical outcomes of such patients. This study aimed to describe our experience in using HFNC in critically ill COVID-19 patients, measure the incidence of EI among patients receiving HFNC treatment for COVID-19-related AHRF, and identify factors that can predict HFNC success or failure.

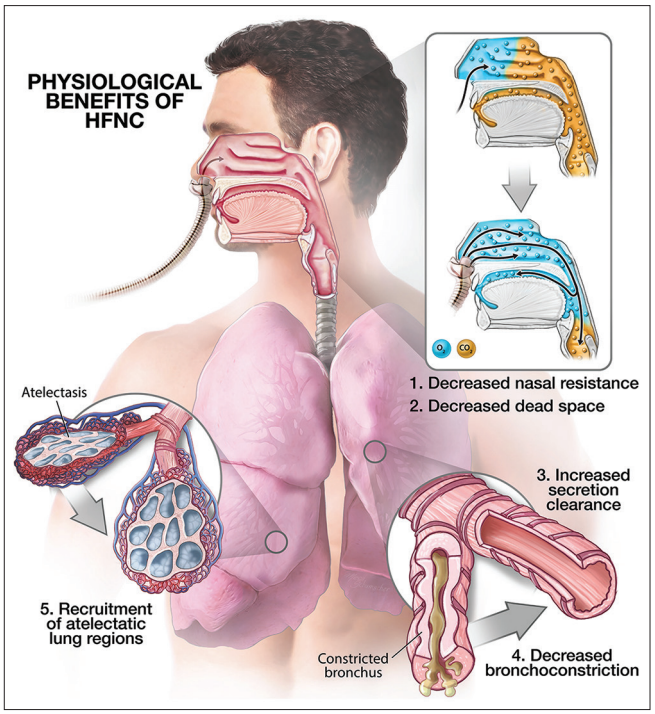

Figure 1: illustration of the physiological benefits of the use of high flow nasal cannula. "Illustration by Mesa Schumacher"

PATIENTS AND METHODS

Study design and settings

This is a single-center, prospective observational cohort study that was conducted in the ICU of a tertiary teaching hospital in the Kingdom of Saudi Arabia from April to August 2020. The study's ethical approval was obtained from the Institutional Review Board of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines.

Study population

All consecutive ICU patients who were diagnosed with COVID-19-related AHRF were screened for eligibility. Patients who experienced COVID-19-related AHRF defined by oxygen saturation (SpO_2) of <92% despite conventional supplemental oxygen and then managed with HFNC were included. 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 who were intubated or received NIV before HFNC application, those requiring intubation as per the treating physician's decision, and patients with "Do Not Resuscitate" orders.

Study procedures

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

All patients with 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, as tolerated. In our ICU, HFNC is delivered using either an AIRVO2 (Fisher and Paykel Healthcare®, Auckland, New Zealand) machine or an Inspired O2FLO (Vincent Medical, Hong Kong, China) machine. Patients were closely monitored for early detection of respiratory deterioration and the need for EI. The HFNC's flow was started from low levels and titrated gradually to 30–60 L/min, as tolerated. The fraction of inspired oxygen (FiO_2) was set to maintain the SpO_2 between 92% and 96%. HFNC failure was defined as the need for EI.

The EI indications were similar to non-COVID-19 acute respiratory failure in an ICU setting, including worsening respiratory status, clinical or laboratory indications of respiratory fatigue, hemodynamic instability, alteration of consciousness, and multiorgan failure. 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 proper personal protective equipments (including, N95 respirator or surgical mask, face shield, safety goggles, gloves, and gown) for all patient encounters, minimizing unnecessary interactions in the ICU, limiting the number of staff in the isolation room, and avoiding aerosol-generating procedures, as possible.

Data collection

Data were collected using pre-designed case report forms that were prospectively filled for all patients. Data were collected by two authors and independently reviewed by a third author. We collected data on demographics, comorbidities, vital signs, arterial blood gases, Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II). Furthermore, the PaO_2/FiO_2 ratio was calculated at ICU admission. We recorded the duration and flow of HFNC, FiO_2, and SpO_2 at several intervals. The application of prone positioning was also recorded. The respiratory rate-oxygenation (ROX) index (ratio of SpO_2/FiO_2 to respiratory rate [RR]) was calculated at the time of 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, and 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). Continuous variables were presented as mean and standard deviation (SD) or median and inter-quartile range (IQR), as appropriate, while categorical variables were displayed as frequencies and percentages. The normality of the data was determined using the Shapiro-Wilk test. Student's *t*-test or Mood's median test were used to compare continuous variables based on normality test results, and Chi-square or Fisher's exact test to assess the difference between categorical variables, as appropriate. The established ROX index cutoff value of 4.88 was used at different time points (2, 6, and 12 hours).[19] Respiratory variables at different points (at the time of HFNC application, 2, 6, 12, and 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 below and above the ROX cutoff point. 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 <0.1 were included in the multivariable Cox regression model. A P value of ≤0.05 was considered statistically significant.

RESULTS

During the study period, a total of 111 ICU patients with confirmed COVID-19 were screened for eligibility. The treating team initiated HFNC treatment in 44 patients (40%) after admission to the ICU. The mean age was 57 ± 14 years,

and six (14%) were females [Table 1]. The median duration of HFNC was 3 days (IQR, 1–5 days), with a median maximum O_2 flow of 60 L/min (IQR, 42–60 L/min) and a median maximum FiO_2 of 95% (IQR, 80–100%).

Twenty-nine (66%) patients experienced HFNC failure and required EI. The median duration from HFNC treatment initiation to EI was 2 days (IQR, 1–7 days). Patients who were successfully weaned from HFNC were significantly younger (P = 0.02). The cohort of patients that failed HFNC therapy had a higher prevalence of comorbidities (i.e., diabetes, hypertension, chronic kidney disease and asthma), but the difference did not reach statistical significance. The PaO_2/FiO_2 ratio at the time of ICU admission was higher in cases of HFNC success than in cases of failure (P = 0.001). The baseline information upon ICU admission and clinical outcomes in a comparison between HFNC success and failure groups is presented in Table 2.

The median ROX score calculated at the time of HFNC 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, 0.023 and 0.042, respectively). The median duration of HFNC treatment was significantly (P = 0.003) longer in successful HFNC cases (5 days; IQR, 4-7 days) than in failed HFNC cases (1 day; IQR, 1-4.5 days).

Oxygen saturation at the initiation of HFNC was higher in the success group (median 96%; IQR, 95–97%). 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 during the first 24 hours. The ROX score improved after 6 hours of HFNC initiation in the success group compared to the failure group. Respiratory variables' measurements during HFNC treatment are presented in Supplementary Table 1.

Table 1: Demographics, comorbidities, and vital signs of patients at ICU admission

Variables	Values (*N*=44)
Age (years), mean±SD	57±14
Male: female ratio	6:1
Smoking, *n* (%)	2 (4)
Comorbidities, *n* (%)	
Diabetes	24 (54)
Hypertension	22 (50)
Bronchial asthma	5 (11)
Chronic kidney disease	5 (11)
Ischemic heart disease	3 (7)
Chronic lung disease	1 (2)
Immunocompromised status	1 (2)
Vital signs	
Systolic/diastolic blood pressure, mean±SD	128±18/76±12 mm Hg
Heart rate, mean±SD	94±17 beats/min
Respiratory rate, mean±SD	31±7 breaths/min
Oxygen saturation, median (IQR)	94 (90–96) %

IQR – Interquartile range; SD – Standard deviation

The AUROC of the ROX index for predicting success at the initiation of HFNC treatment was 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) after 24 hours. The AUROC for SpO_2 after 2 hours of HFNC initiation was 0.64 (CI, 0.41–0.87) and after 12 hours was 0.646 (CI, 0.42–0.88). In contrast, the RR and FiO_2 did not show good predictive capacity for HFNC failure. Supplementary Table 2 presents the accuracy of different respiratory variables for the prediction of HFNC success.

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 [Figure 2]. The ROX score at 2 hours showed that patients with a score of ≥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, PaO_2/FiO_2 ratio, and prone position), a high SOFA score and a low ROX index significantly predicted the HFNC failure [Table 3].

The overall mortality rate for patients who failed HFNC was 52%. The median ICU LOS for the successfully weaned HFNC group was 6 days (IQR, 6-11 days), while the HFNC failure group had a median of 11 days (IQR, 6-17 days). HFNC treatment failure was significantly associated with higher in-hospital mortality and a longer ICU LOS (P = 0.001 and 0.043, respectively).

DISCUSSION

In this prospective observational study, 66% of patients receiving HFNC required EI. Moreover, we found that a high SOFA score and a low ROX index were associated with HFNC failure.

Multiple retrospective observational studies reported an HFNC failure rate ranging between 32%–72%.[13-16,20,21] The high variability in the reported HFNC failure rates might

Table 2: Comparison of baseline information of patients at ICU admission and overall clinical outcome

Variables	HFNC success (*n*=15)	HFNC failure (*n*=29)	*P*
Demographics			
Age (years), mean±SD	50.67±12.92	60.21±13.47	0.029*
Male: female ratio	6.5:1	6:1	0.673
Comorbidities, *n* (%)			
Diabetes	7 (47)	17 (59)	0.45
Hypertension	7 (47)	15 (52)	0.5
Bronchial asthma	1 (7)	4 (14)	0.437
Chronic kidney disease	1 (7)	4 (14)	0.437
Ischemic heart disease	1 (7)	2 (7)	0.736
Chronic lung disease	1 (7)	0	0.341
Immunocompromised status	1 (7)	0	0.341
Respiratory variables			
ROX score, mean±SD	5.16±2.2	4.06±1.49	0.055
APACHE-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 (mmHg), mean±SD	96.07±67.04	43.31±35.11	0.001*
Respiratory rate, mean±SD	27.8±6.44	32.1±6.46	0.042*
Awake prone positioning combined with HFNC, *n* (%)	11 (73)	21 (75)	1
30-day outcomes			
Death, *n* (%)	0	15 (52)	0.001*
Discharged or still in ICU, *n* (%)	15 (100)	14 (48)	
ICU LOS (days), median (IQR)	6 (6–11)	11 (6–17)	0.043
Hospital LOS (days), median (IQR)	17 (14–26)	14 (8–20)	0.477

*Significant at 0.05 level of significance. APACHE-II – Acute Physiology and Chronic Health Evaluation II; HFNC – High-flow nasal cannula; ICU – Intensive care unit; IQR – Interquartile range; LOS – Length of stay; PaO_2/FiO_2 – Arterial partial pressure of oxygen/fraction of inspired oxygen; ROX – Respiratory rate-oxygenation; SD – Standard deviation; SOFA – Sequential organ failure assessment

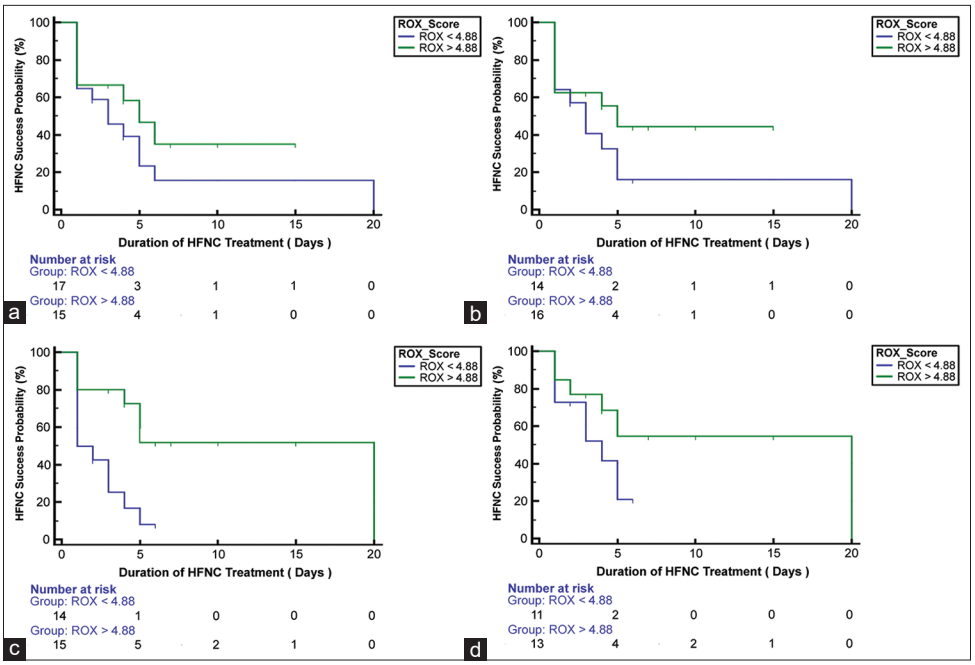

Figure 2: Kaplan–Meier plots demonstrating HFNC success probability stratified at different time intervals after HFNC treatment; (a) ROX score at 2 h. (b) ROX score at 6 h. (c) ROX score at 12 h. (d) ROX score at 18 h. ROX – Respiratory rate-oxygenation; HFNC – High-flow nasal cannula

be attributed to several possible explanations. For instance, the definition of failure was not standardized; few studies defined failure as the need for NIV, EI, or death,[13,16] one study defined failure as the need for NIV or EI[14], while others, including our study, defined failure as the need for EI only.[15,20,21] Furthermore, the threshold for intubation varies among intensivists due to a lack of consensus on determining HFNC failure. Moreover, illness severity and the imbalance between baseline characteristics of patients varied between aforementioned studies.

Our study confirmed the observation of previous studies, where mortality was higher in cases of HFNC failure than in cases of success (52% versus 0%). Thus, clinicians treating hypoxemic COVID-19 patients should identify patients with a higher likelihood of benefiting from HFNC.

Table 3: Regression analysis for the prediction of high-flow nasal cannula failure

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
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. APACHE-II – Acute Physiology and Chronic Health Evaluation II; CI – Confidence interval; HR – Hazard ratio; PaO_2/FiO_2 – Arterial partial pressure of oxygen/fraction of inspired oxygen; ROX – Respiratory rate-oxygenation; SOFA – Sequential organ failure assessment

Roca *et al*.[19] found that the ROX index predicts HFNC failure in patients with AHRF secondary to pneumonia. 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.

Our study measured the ROX index at the time of HFNC initiation 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. This study adds to the existing knowledge by showing the potential utility of the previously established cutoff of the ROX index for monitoring HFNC treatment in COVID-19-related AHRF. After adjustment for other confounders, the ROX index and SOFA score were still strong predictors of HFNC treatment failure. The baseline PaO_2/FiO_2 ratio was higher in successfully weaned HFNC cases. In terms of the baseline characteristics upon ICU admission, the prevalence of diabetes, hypertension, chronic kidney disease, and asthma was higher in patients with HFNC failure; however, the difference was not statistically significant.

Similarly, another study that included 62 patients with COVID-19-related AHRF showed that a ROX index measured after 4 hours of HFNC was significantly associated with HFNC success and a low risk of EI.[20] Another study showed that a PaO_2/FiO_2 ≤100 mm Hg at ICU admission was a significant predictor of HFNC failure.[13] Wang *et al*.[14] study demonstrated that none of the patients with PaO_2/FiO_2 >200 mm Hg had HFNC failure compared to 63% failure in patients with low PaO_2/FiO_2 (≤200 mm Hg). In addition, the RR was found to decrease significantly after 1–2 hours of HFNC use in successful cases.[14]

A 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 confounding factors, longer duration from ICU admission to EI was not associated with increased mortality in their cohort.[15]

A multicenter retrospective study that included 43 patients treated with HFNC reported a success rate of HFNC treatment to be 53.5%.[16] While the overall hospital mortality of that cohort was 32.9%, the hospital mortality rate for failed HFNC was 65%.[16] Male sex and low SpO_2 at admission were independent predictors of HFNC failure.[16] Moreover, another study demonstrated that a RR ≥26/min after 30-minutes of HFNC application to be associated with a higher risk of HFNC failure.[22] However, the study was limited by the small sample size (30 patients) and high SpO_2 (100%) observed in a third of their cohort, which could participate in decreasing the contribution of SpO_2/FiO_2 in the ROX's diagnostic accuracy.[22]

Ferrando *et al*.[23] have examined the use of HFNC with awake prone positioning, in which they reported that 82 patients (41%) required EI. 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.[23] Similarly, in our cohort, there was no significant difference in the probability of HFNC success versus failure when awake prone positioning combined with HFNC. Nevertheless, HFNC remains an effective modality of respiratory support, in which Ferrando *et al*.[23] reported 117 patients (59%) of 199 patients on HFNC did not require EI.

A prospective multicenter study that involved 293 patients has reported a 53% HFNC failure rate. They found a high ROX index at 6 hours to be significantly associated with HFNC success. However, patients who failed HFNC treatment had very high mortality (92%).[24] This considerably high rate is inconsistent with previous studies and the current study findings, which might be attributed to several reasons, including resource-constrained setting, the majority (64%) of their cohort were admitted to a non-critical care environment and limited ICU expertise. Besides, there was a significant difference between the admitting settings of the two groups, where 45% of successfully treated patients were admitted to the ICU setting compared to only 28% of the failed HFNC cases.[24] Although this study adds great value to the

literature, it 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 setting with optimal monitoring.

Noteworthy, infectious aerosolization fears were significantly prominent during the early stage of the COVID-19 pandemic.[25] However, multiple studies generated a cumulative low-moderate quality of evidence, which indicate a relatively low risk of dispersing a significant amount of bio-aerosol particles and suggest no increase in the risk of infection transmission to healthcare workers with an excellent fitted HFNC, good sealing circuit, and appropriate adherence to airborne precautions.[26-31] Yet, high-quality evidence on the risk of airborne contamination and nosocomial infection with the use of HFNC for the management of COVID-19 patients is needed.

These findings indicate that with the application of appropriate selection criteria, a significant number of patients with COVID-19-related AHRF could avoid EI. However, HFNC therapy should not be provided to patients at a high risk of failure due to increased mortality. Furthermore, appropriate infection prevention and control policies need to be applied to prevent potential nosocomial spread.

This study has several strengths. It is one of few studies investigating the use of HFNC in AHRF secondary to COVID-19, which can be a useful and safe intervention for appropriately selected patients in a pandemic situation. Moreover, 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 to help physicians and respiratory therapists select patients with the best chance of success and not delay EI when necessary. Further strengthening point is the adherence of the treating team with guidelines issued by the Saudi Critical Care Society and Surviving 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 few limitations. The study's observational nature, lack of a control arm, and a small sample size are important limiting factors. Furthermore, as 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

In this prospective cohort study, one-third of the hospitalized COVID-19 patients who received HFNC did not require intubation. However, HFNC failure was associated with a higher in-hospital mortality. Therefore, optimal patient selection for HFNC treatment, 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.

Acknowledgments

The authors would like to thank all the ICU healthcare workers involved in COVID-19 patient care.

Ethical approval

The Institutional Review Board (IRB) at Imam Abdulrahman Bin Faisal University provided ethical approval for this study (Ref. no.: IRB-2020-01-276). Because of extenuating circumstances and the observational nature of the study, the waiver of written informed consent process was approved by the IRB. This cohort study followed the institutional and national research committees' ethical standards and was adherent with the Declaration of Helsinki, 2013.

Permissions

Appropriate permission was secured. Written permission for exclusive right from the copyright holder of Figure 1 is fully granted, including the exclusive right to publish and distribute the article and grant rights to others, including commercial purposes. Moreover, it includes the authority to enforce the rights in the article, on behalf of the authors, against third parties, in the case of plagiarism or copyright infringement.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, *et al*. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185-96.
2. Jones PG, Kamona S, Doran O, Sawtell F, Wilsher M. Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: The HOT-ER study. Respir Care 2016;61:291-9.

3. Lee CC, Mankodi D, Shaharyar S, Ravindranathan S, Danckers M, Herscovici P, *et al.* High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: A systematic review. Respir Med 2016;121:100-8.
4. Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, *et al.* High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: A systematic review and meta-analysis. Intensive Care Med 2019;45:563-72.
5. Rello J, Pérez M, Roca O, Poulakou G, Souto J, Laborda C, *et al.* CRIPS investigators: High-flow nasal therapy in adults with severe acute respiratory infection: A cohort study in patients with 2009 influenza A/H1N1v. J Crit Care 2012;27:434-9.
6. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: Mechanisms of action and clinical implications. Chest 2015;148:253-61.
7. Ischaki E, Pantazopoulos I, Zakynthinos S. Nasal high flow therapy: A novel treatment rather than a more expensive oxygen device. Eur Respir Rev 2017;26:170028.
8. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
9. Cheung JC, Ho LT, Cheng JV, Cham EY, Lam KN. Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med 2020;8:e19.
10. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052-9.
11. Xie J, Wu W, Li S, Hu Y, Hu M, Li J, *et al.* Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: A retrospective multicenter study. Intensive Care Med 2020;46:1863-72.
12. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, *et al.* Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50:16024-26.
13. Vianello A, Arcaro G, Molena B, Turato C, Sukthi A, Guarnieri G, *et al.* High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection. Thorax 2020;75:998-1000.
14. Wang K, Zhao W, Li J, Shu W, Duan J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. Ann Intensive Care 2020;10:37.
15. Hernandez-Romieu AC, Adelman MW, Hockstein MA, Robichaux CJ, Edwards JA, Fazio JC, *et al.* Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: A single-center cohort study. Crit Care Med 2020;48:e1045-53.
16. Xia J, Zhang Y, Ni L, Chen L, Zhou C, Gao C, *et al.* High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: A multicenter, retrospective cohort study. Crit Care Med 2020;48:e1079-86.
17. Alhazzani W, Al-Suwaidan FA, Al Aseri ZA, Al Mutair A, Alghamdi G, Rabaan AA, *et al.* The Saudi critical care society clinical practice guidelines on the management of COVID-19 patients in the intensive care unit. Saudi Crit Care J 2020;4:27-44.
18. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, *et al.* Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.
19. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, *et al.* An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med 2019;199:1368-76.
20. Zucman N, Mullaert J, Roux D, Roca O, Ricard JD, Contributors. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. Intensive Care Med 2020;46:1924-6.
21. Chandel A, Patolia S, Brown AW, Collins AC, Sahjwani D, Khangoora V, *et al.* High-flow nasal cannula therapy in COVID-19: Using the ROX index to predict success. Respir Care 2021;66:909-19.
22. Blez D, Soulier A, Bonnet F, Gayat E, Garnier M. Monitoring of high-flow nasal cannula for SARS-CoV-2 severe pneumonia: Less is more, better look at respiratory rate. Intensive Care Med 2020;46:2094-5.
23. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, *et al.* Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: A multicenter, adjusted cohort study. Crit Care 2020;24:597.
24. Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, *et al.* The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. EClinicalMedicine 2020;28:100570.
25. Alshaqaq HM, Al Aseri ZA, Alshahrani MS. High-flow nasal cannula for patients with COVID-19 acute hypoxemic respiratory failure. Saudi Crit Care J 2020;4:6-9.
26. Hui DS, Chow BK, Lo T, Tsang OT, Ko FW, Ng SS, *et al.* Exhaled air dispersion during high-flow nasal cannula therapy *versus* CPAP *via* different masks. Eur Respir J 2019;53:1802339.
27. Gaeckle NT, Lee J, Park Y, Kreykes G, Evans MD, Hogan CJ Jr. Aerosol generation from the respiratory tract with various modes of oxygen delivery. Am J Respir Crit Care Med 2020;202:1115-24.
28. Jermy MC, Spence CJ, Kirton R, O'Donnell JF, Kabaliuk N, Gaw S, *et al.* Assessment of dispersion of airborne particles of oral/nasal fluid by high flow nasal cannula therapy. PLoS One 2021;16:e0246123.
29. Roca O, Pacheco A, Rodon J, Antón A, Vergara-Alert J, Armadans L, *et al.* (in press). Nasal high flow oxygen therapy in COVID-19 patients does not cause environmental surface contamination. J Hosp Infect 2021.
30. Westafer LM, Soares WE 3rd, Salvador D, Medarametla V, Schoenfeld EM. No evidence of increasing COVID-19 in health care workers after implementation of high flow nasal cannula: A safety evaluation. Am J Emerg Med 2021;39:158-61.
31. Bem RA, van Mourik N, Klein-Blommert R, Spijkerman IJ, Kooij S, Bonn D, *et al.* Risk of aerosol formation during high-flow nasal cannula treatment in critically ill subjects. Respir Care 2021;66:891-6.

Supplementary Table 1: The effect of respiratory variables during high-flow nasal cannula treatment

Variables	Measurement time	HFNC success (median IQR) (*n*=15)	HFNC failure (median IQR) (*n*=29)	*P*
SpO_2, *n* (%)	At the start of HFNC	96 (95–97)	92 (90–96)	0.005*
	After 2 h	96 (94–97)	93 (90–96)	0.194
	After 6 h	95 (91–96)	94 (90–96)	0.969
	After 12 h	95 (93–97)	93 (90–96)	0.236
	After 18 h	95 (93–98)	95 (90–97)	0.07
	After 24 h	96 (95–96)	94 (90–98)	0.680
RR (bpm)	At the start of HFNC	23 (20–27)	30 (23–36)	0.048*
	After 2 h	25 (20–32)	27 (23–32)	0.794
	After 6 h	25 (22–28)	25 (20–31)	1
	After 12 h	24 (21–29)	27 (22–30)	0.245
	After 18 h	24 (23–27)	26 (22–33)	0.214
	After 24 h	21 (20–24)	25 (20–30)	0.036*
FiO_2, *n* (%)	At the start of HFNC	75 (60–100)	90 (60–100)	0.198
	After 2 h	75 (60–100)	90 (80–100)	0.303
	After 6 h	75 (60–95)	95 (80–100)	0.209
	After 12 h	70 (60–90)	95 (80–100)	0.173
	After 18 h	75 (60–100)	90 (70–100)	0.140
	After 24 h	70 (60–100)	90 (70–100)	0.140
ROX	At the start of HFNC	4.98 (3.94–7.8)	3.69 (2.96–4.96)	0.078
	After 2 h	4.95 (3.29–8.0)	4.02 (3.46–5.11)	0.143
	After 6 h	5.05 (4.25–5.8)	4.09 (3.16–6.1)	0.245
	After 12 h	5.80 (5.18–6.28)	3.53 (3.14–5.0)	0.021*
	After 18 h	4.94 (4.01–6.4)	3.60 (2.86–6.3)	0.685
	After 24 h	6.05 (4.56–7.1)	4.7 (2.86–6.4)	0.408

*Significant at 0.05 level of significance. bpm – Breaths per minute; FiO_2 – Fraction of inspired oxygen; HFNC – High-flow nasal cannula; IQR – Interquartile range; ROX – Respiratory rate-oxygenation; RR – Respiratory rate; SpO_2 – Oxygen saturation

Supplementary Table 2: Accuracy of different respiratory variables at different time points for the prediction of high-flow nasal cannula success

Variables	Measurement time	AUROC (95% CI)	*P*
SpO_2	At the start of HFNC	0.619 (0.383–0.855)	0.336
	After 2 h	0.638 (0.409–0.868)	0.264
	After 6 h	0.481 (0.239–0.722)	0.877
	After 12 h	0.646 (0.416–0.876)	0.239
	After 18 h	0.569 (0.329–0.809)	0.577
	After 24 h	0.581 (0.324–0.838)	0.515
RR	At the start of HFNC	0.208 (0.011–0.404)	0.018*
	After 2 h	0.423 (0.174–0.672)	0.535
	After 6 h	0.4 (0.163–0.637)	0.42
	After 12 h	0.392 (0.156–0.629)	0.385
	After 18 h	0.381 (0.147–0.615)	0.336
	After 24 h	0.304 (0.079–0.528)	0.114
FiO_2	At the start of HFNC	0.351 (0.163–0.538)	0.132
	After 2 h	0.357 (0.168–0.547)	0.149
	After 6 h	0.351 (0.166–0.536)	0.132
	After 12 h	0.33 (0.146–0.514)	0.086
	After 18 h	0.39 (0.198–0.583)	0.268
	After 24 h	0.367 (0.175–0.559)	0.178
ROX	At the start of HFNC	0.792 (0.596–0.988)	0.021*
	After 2 h	0.646 (0.399–0.892)	0.249
	After 6 h	0.633 (0.389–0.878)	0.291
	After 12 h	0.746 (0.523–0.969)	0.052
	After 18 h	0.608 (0.364–0.852)	0.391
	After 24 h	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; FiO_2 – Fraction of inspired oxygen; HFNC – High-flow nasal cannula; ROX – Respiratory rate-oxygenation; RR – Respiratory rate; SpO_2 – Oxygen saturation