High-Flow Nasal Cannula Therapy in COVID-19: Using the ROX Index to Predict Success

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BACKGROUND: Optimal timing of mechanical ventilation in COVID-19 is uncertain. We sought to evaluate outcomes of delayed intubation and examine the ROX index (ie, $[S_{pO_2}/F_{IO_2}]$/breathing frequency) to predict weaning from high-flow nasal cannula (HFNC) in patients with COVID-19. METHODS: We performed a multicenter, retrospective, observational cohort study of subjects with respiratory failure due to COVID-19 and managed with HFNC. The ROX index was applied to predict HFNC success. Subjects that failed HFNC were divided into early HFNC failure (≤ 48 h of HFNC therapy prior to mechanical ventilation) and late failure (> 48 h). Standard statistical comparisons and regression analyses were used to compare overall hospital mortality and secondary end points, including time-specific mortality, need for extracorporeal membrane oxygenation, and ICU length of stay between early and late failure groups. RESULTS: 272 subjects with COVID-19 were managed with HFNC. One hundred sixty-four (60.3%) were successfully weaned from HFNC, and 111 (67.7%) of those weaned were managed solely in non-ICU settings. ROX index >3.0 at 2, 6, and 12 hours after initiation of HFNC was 85.3% sensitive for identifying subsequent HFNC success. One hundred eight subjects were intubated for failure of HFNC (61 early failures and 47 late failures). Mortality after HFNC failure was high (45.4%). There was no statistical difference in hospital mortality (39.3% vs 53.2%, $P = .18$) or any of the secondary end points between early and late HFNC failure groups. This remained true even when adjusted for covariates. CONCLUSIONS: In this retrospective review, HFNC was a viable strategy and mechanical ventilation was unecessary in the majority of subjects. In the minority that progressed to mechanical ventilation, duration of HFNC did not differentiate subjects with worse clinical outcomes. The ROX index was sensitive for the identification of subjects successfully weaned from HFNC. Prospective studies in COVID-19 are warranted to confirm these findings and to optimize patient selection for use of HFNC in this disease. *Key words: COVID-19; SARS-CoV-2; high-flow nasal cannula; hypoxemic respiratory failure; viral pneumonia; respiratory insufficiency.* [Respir Care 2021;66(6):909–919. © 2021 Daedalus Enterprises]

Introduction

Patients with coronavirus disease 2019 (COVID-19) face substantial morbidity and mortality related to viral pneumonitis that can progress to ARDS.[1] The optimal management strategy for respiratory failure related to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still evolving. Patients with COVID-19 who require mechanical ventilation are at high risk for poor outcomes and have a likelihood of mortality estimated at approximately 40%.[2]

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Though overall mortality of the disease, including the mortality of patients in the ICU, has decreased over the course of the pandemic, COVID-19 remains a significant burden on the worldwide health care infrastructure.[3] Mortality may be related to the progressive course of the viral infection, but it could be perpetuated by the inherent complications of mechanical ventilation itself.

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High-flow nasal cannula (HFNC) devices can deliver warmed, humidified oxygen at flows up to 60 L/min and F_{IO_2} up to 1.0. This modality of oxygen delivery can reduce the need for intubation and mechanical ventilation for patients with acute hypoxemic respiratory failure.[4,5] Data also suggest that early use of this therapy may decrease the need for invasive mechanical ventilation in COVID-19.[6] Success of HFNC can be predicted by the ROX index (ie, $[S_{pO_2}/F_{IO_2}]$/breathing frequency), which is a score that has been validated in the treatment of pneumonia and ARDS. This clinical score was initially applied based on clinical data at 2 h, 6 h, and 12 h after application of HFNC.[7] The score has been subsequently applied to the use of HFNC in the treatment of COVID-19, and investigators have proposed values that correlate with subsequent failure of HFNC and need for endotracheal intubation.[8-11] Most prior research related to HFNC use in patients with COVID-19 has focused efforts on utilizing the ROX index to identify patients at risk of subsequent endotracheal intubation, and data regarding the use of the index to select patients who may ultimately be weaned from HFNC are lacking.

Substantial controversy exists as to the optimal timing of initiation of invasive mechanical ventilation in the management of COVID-19 respiratory failure. Some have argued for more aggressive, early intubation to avoid possible patient self-induced lung injury.[12-14] Others have advocated for longer trials of noninvasive supplemental oxygen modalities as a means to avoid endotracheal intubation and associated complications.[15,16] Thus, despite possible hazards associated with delayed intubation, many clinicians have utilized extended trials of HFNC in patients with COVID-19 respiratory failure.[16,17] The aim of this study was to evaluate predictors of successful weaning and overall outcomes in subjects managed with HFNC for the support of respiratory failure related to COVID-19.

QUICK LOOK

Current knowledge

High-flow nasal cannula (HFNC) is routinely used as part of the care of patients with respiratory failure related to COVID-19. Significant debate exists as to the optimal timing of progression to invasive mechanical ventilation in the event of clinical worsening or failure to wean from HFNC.

What this paper contributes to our knowledge

In this multicenter, observational, cohort study, HFNC was frequently successful in avoiding the need for invasive mechanical ventilation. The ROX index (ie, $[S_{pO_2}/F_{IO_2}]$/breathing frequency) was sensitive for the identification of subjects who could be managed with HFNC without the subsequent need for endotracheal intubation. Clinical outcomes did not differ between subjects based on the duration of HFNC therapy prior to the initiation of mechanical ventilation. Extended use of HFNC may be reasonable in the care of patients with COVID-19 as a measure to avoid invasive mechanical ventilation.

Methods

Study Population

We performed a multicenter, retrospective, observational study of subjects treated for acute respiratory failure secondary to COVID-19 and managed with HFNC within the Inova Health System. The Inova Health System consists of 5 hospitals, including a large tertiary care center and 4 community hospitals. Subjects were included if they were ≥ 18 y old, had a laboratory-confirmed diagnosis of COVID-19 by polymerase chain reaction testing, and were treated with HFNC for ≥ 2 h. Patients were excluded if endotracheal intubation was performed prior to initiation of HFNC (eg, following extubation to reduce the risk of re-intubation) or performed on an elective basis (eg, for elective surgical care). To minimize heterogeneity of the studied population, patients who were switched to noninvasive ventilation prior to endotracheal intubation were also excluded. Given the objective to compare outcomes associated with early versus late endotracheal intubation, patients for whom endotracheal intubation was not within their goals of care were also excluded.

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The authors have disclosed no conflicts of interest.

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Data were collected for subjects admitted to the Inova Health System between March 1, 2020, and June 9, 2020. The study was approved by the institutional review board (U20-06-4134) at Inova Fairfax Hospital. All data were collected from the electronic medical record.

Inova Health System's COVID-19 Management Protocol

The strategy for the management of acute respiratory failure was fairly homogenous across our health care system. Efforts were made to avoid intubation where feasible with the use of HFNC (Optiflow, Fisher & Paykel, Auckland, New Zealand). Noninvasive ventilation was largely avoided early on due to concerns regarding aerosolizing the SARS-CoV-2 virus but was increasingly utilized over time. Inhaled nitric oxide was delivered in a blend with oxygen via HFNC, and self-proning was incorporated where deemed clinically appropriate. Failure of HFNC was defined as the need for mechanical ventilation despite HFNC application. The need for endotracheal intubation after HFNC was at the discretion of the treating clinician, but it was generally based on the presence of hypoxemia with a failure to maintain $S_{pO_2} > 88\%$ despite receiving the maximum F_{IO_2} allowed by the HFNC, breathing frequency > 35 breaths/min with associated respiratory distress, severe metabolic acidosis, cardiopulmonary arrest, or altered mental status requiring intubation for avoidance of aspiration. In the event of the need for mechanical ventilation, subjects were typically managed initially with moderate PEEP (10–12 cm H_2O) and a lung-protective ventilator strategy. Neuromuscular blockade and prone positioning were frequently utilized in subjects with severe ARDS. The choice of sedation and analgesia was at the discretion of the attending intensivist and was targeted to a Richmond Agitation Sedation Scale of 0 to –2.[18] Subjects were considered for extracorporeal membrane oxygenation (ECMO) if they were < 60 y old, were on invasive mechanical ventilation for < 10 d, had $S_{pO_2}/F_{IO_2} < 100$, and failed lung-protective ventilation despite neuromuscular blockade and prone positioning.

Adjunct therapeutics targeting COVID-19 disease were administered at the discretion of the attending physician and commonly included systemic glucocorticoids and remdesivir. The use of convalescent plasma was infrequent during the study period. Given high patient volumes related to the COVID-19 pandemic across the Inova Health system, changes in the usual protocol for treatment and monitoring of patients with respiratory failure at our facilities were necessary. All patients managed with invasive mechanical ventilation were treated in an intensive care environment. However, expansion of the level of acuity managed outside of an intensive care setting was required, and many subjects were managed with HFNC in augmented step-down units up to the point of requiring endotracheal intubation.

Data Collection

Data were abstracted in a structured format by 3 of the authors (AC, SP, and DS), including demographics, comorbid diseases (as documented in the admitting history and physical), and clinical data (eg, vital signs within 1 h prior to HFNC application and for 12 h thereafter, common laboratory results, and illness severity as estimated with the Sequential Organ Failure Assessment [SOFA]). The ROX index was calculated and recorded at 2 h, 6 h, and 12 h after HFNC application. Laboratory data were collected when available within 6 h of initiation of HFNC. Adjunctive measures provided while subjects were receiving HFNC, such as the use of prone positioning or the administration of inhaled nitric oxide, remdesivir, or systemic steroids (ie, the equivalent of prednisone ≥ 20 mg/d) were also recorded. The primary outcome examined was overall hospital mortality. Secondary outcomes included the need for ECMO, mortality at 14 d and at 28 d after HFNC and endotracheal intubation, and ICU length of stay. Data were also collected and compared for ICU-related complications, including the development of ventilator-associated pneumonia (ie, a combination of new or progressive radiographic infiltrate with a positive respiratory specimen and a clinically documented diagnosis), pneumothorax, secondary infection (ie, a positive culture or related microbiologic data thought to be pathologic by the treating clinician), acute kidney injury (ie, a rise in serum creatinine of ≥ 0.3 mg/dL over 48 h), need for renal replacement therapy, and imaging-confirmed venous thromboembolism (ie, based on the finalized radiographic report or documented point-of-care ultrasound findings in subjects with acute decompensation and suspected pulmonary embolism).

Subjects were first divided into those managed with HFNC who were successfully weaned from this modality and those who were ultimately intubated. Those who underwent endotracheal intubation after HFNC failure were then divided into 2 groups; early failure (defined as ≤ 48 h of HFNC therapy prior to endotracheal intubation) and late failure (intubation after > 48 h of HFNC therapy).

Statistical Analysis

Distribution of all continuous data were examined for normality using visual inspection and the Wilk-Shapiro test. Characteristics of the groups are presented using the mean ± SD for normally distributed data and compared between groups using the 2-sample *t* test. Data that were not normally distributed are presented as median (interquartile range) and compared using the Wilcoxon rank-sum test. Categorical data are presented as counts with proportions and compared using the Fisher exact test (2-tailed). The diagnostic accuracy of the ROX index to predict success of HFNC (ie, application without subsequent need for

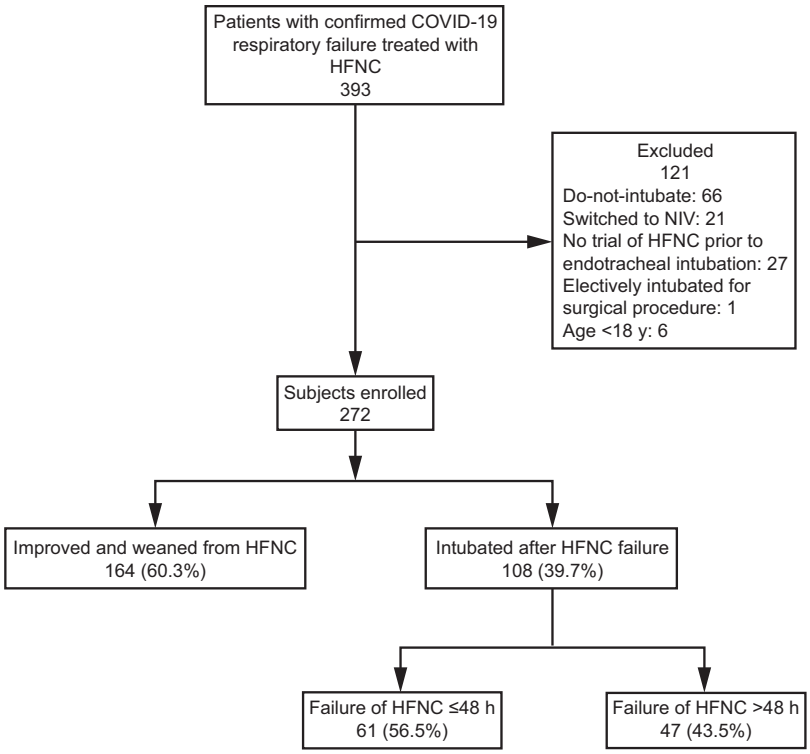

Figure 1. Flow chart. HFNC = high-flow nasal cannula, NIV = noninvasive ventilation.

mechanical ventilation) is presented using a receiver operating characteristic curve together with sensitivity, specificity, and predictive values at the defined cutoffs, and summarized using the area under the curve together with the 95% CI. To compare clinical outcomes between early and late HFNC failure, we performed logistic regression (overall ICU mortality, 14-d mortality, and 28-d mortality). ICU length of stay demonstrated a positively skewed distribution. To minimize the effects of outliers and to account for this distribution, negative binomial regression was utilized to compare this outcome. P values $< .05$ were considered statistically significant. Univariate and multivariate logistic regression analysis of factors possibly associated with mortality were performed. Variables were included in the model if they were statistically significant based on univariate analysis and subsequently removed by means of the stepwise backward elimination method with $P < .15$. Outcome data were available for all subjects at the time of analysis. Any missing clinical data were handled via complete case analysis (only cases with available data were analyzed). All statistical analyses were performed using STATA 14 (StataCorp, College Station, Texas).

Results

During the study period, our search strategy identified 393 subjects with respiratory failure secondary to COVID-19 who required the use of HFNC within the Inova Health System. Patients who did not receive HFNC therapy prior to endotracheal intubation ($n = 27$), were switched to noninvasive ventilation ($n = 21$), were intubated for an elective reason ($n = 1$), or were < 18 y old ($n = 6$) were excluded. Given that the primary study objective was to analyze the outcomes of subjects who ultimately underwent endotracheal intubation, 66 patients were excluded as intubation and mechanical ventilation did not align with their goals of care. Of the remaining 272 subjects, 164 (60.3%) recovered without intubation and were weaned successfully from HFNC, whereas 108 (39.7%) subjects were intubated after failing HFNC, with 61 intubated after ≤ 48 h of HFNC and 47 intubated after > 48 h of HFNC application (Fig. 1).

The characteristics of the 164 subjects managed with HFNC who were successfully weaned from this modality are presented in Table 1. Compared to those who underwent intubation, subjects who were successfully weaned from HFNC were more likely to be younger and have no comorbidities. A history of active cancer, higher initial SOFA score, higher lactate, higher procalcitonin, and lower neutrophil to lymphocyte ratio were all associated with subsequent failure of HFNC. Subjects weaned successfully from HFNC received this therapy for longer and had a higher median ROX index at the defined cutoffs compared to those subjects who required mechanical ventilation. None of the subjects successfully weaned from HFNC died prior to hospital discharge. Receiver operator curves based on the ROX index were estimated at 2 h, 6 h, and 12 h after initiation of HFNC

Table 1. Baseline Characteristics of Subjects Treated With HFNC

	All Subjects ($n = 272$)	Weaned from HFNC ($n = 164$)	HFNC Failure ($n = 108$)	P
Age, y	57 ± 13	54 ± 14	60 ± 13	< .001
Female	92 (33.8)	60 (36.6)	32 (29.6)	.24
Race, non-White	248 (91.2)	154 (93.9)	94 (87.0)	.08
Body mass index, kg/m^2	28.7 (25.2–33.4)	28.6 (25.5–33.2)	28.7 (24.9–33.6)	.90
HFNC duration, d	3 (1–6)	4 (2–7)	2 (1–4)	< .001
Comorbid diseases				
No comorbid disease	83 (3.5)	60 (36.6)	23 (21.3)	.01
Hypertension	116 (42.6)	64 (39.0)	52 (48.1)	.17
Diabetes mellitus	101 (37.1)	56 (34.1)	45 (41.7)	.25
Chronic kidney disease	20 (7.4)	8 (4.9)	12 (11.1)	.061
End-stage renal disease	8 (2.9)	4 (2.4)	4 (3.7)	.72
Coronary artery disease	9 (3.3)	5 (3.0)	4 (3.7)	.74
Hyperlipidemia	74 (27.2)	40 (24.4)	34 (31.5)	.21
Asthma	13 (4.8)	9 (5.5)	4 (3.7)	.57
COPD	2 (0.7)	1 (0.6)	1 (0.9)	> .99
Active cancer	7 (2.6)	1 (0.6)	6 (5.6)	.02
HFrEF	4 (1.5)	2 (1.2)	2 (1.9)	.65
Systemic anticoagulation	9 (3.3)	8 (4.9)	1 (0.9)	.09
Clinical data at HFNC initiation				
Heart rate, beats/min	93 (80–104)	89 (80–103)	95 (82–104)	.19
Mean arterial pressure, mm Hg	89.7 ± 13.0	89.3 ± 12.9	9.3 ± 13.2	.57
Breathing frequency, breaths/min	29 (24–36)	28 (24–36)	30 (26–37)	.059
Oxygen saturation	93 (90–96)	93 (90–96)	93 (89–95)	.22
SOFA score	3 (1–5)	2 (1–4)	4 (2–7)	< .001
White blood cells, $\times 10^9$ per mL	8.3 (6.0–11.4)	8.0 (6.0–1.9)	8.9 (6.1–11.6)	.40
Neutrophil to lymphocyte ratio	6.5 (4.2–11.7)	6.1 (3.9–1.6)	8.1 (4.9–12.0)	.02
Lactate, mmol/L	1.7 (1.3–2.3)	1.5 (1.3–2.1)	1.9 (1.4–2.8)	< .005
C-reactive protein, mg/L	16.8 (10.0–24.2)	16.7 (9.8–23.6)	17.2 (1.8–26.3)	.51
D-dimer, μg/mL	1.3 (0.9–2.5)	1.3 (0.8–2.2)	1.3 (0.9–2.7)	.25
Procalcitonin, ng/mL	0.3 (0.1–0.6)	0.2 (0.1–0.5)	0.3 (0.1–1.0)	.033
ROX index				
2 h after HFNC	4.5 (3.3–6.0)	4.9 (3.7–6.7)	3.6 (2.8–4.8)	< .001
6 h after HFNC	4.6 (3.6–6.3)	5.1 (4.1–6.9)	3.9 (3.0–4.8)	< .001
12 h after HFNC	4.7 (3.4–6.2)	5.3 (4.3–6.9)	3.8 (2.6–4.5)	< .001

Data presented as mean ± SD, median (interquartile range), or n (%) unless otherwise indicated.
HFNC = high-flow nasal cannula
HFrEF = heart failure with reduced ejection fraction
SOFA = Sequential Organ Failure Assessment

to predict the success of HFNC. Overall diagnostic accuracy was good, and this improved with a longer duration of HFNC application (Fig. 2). The diagnostic accuracy of a ROX index at 12 h was the best (area under the curve 0.78 [95% CI 0.72–0.84]), and an index of > 3.67 had a sensitivity of 84.1%, specificity of 49.4%, positive predictive value of 71.5%, and a negative predictive value of 67.1% for predicting success of HFNC, thus satisfying the closest-to-(0,1) criterion for threshold selection. For subjects who were not intubated or weaned from HFNC within the first 12 h after HFNC initiation, a ROX index > 3.0 at each time point (ie, 2 h, 6 h, and 12 h) had a sensitivity of 85.3%, specificity of 51.1%, positive predictive value of 75.5%, and a negative predictive value of 66.7% for the subsequent success of HFNC.

The characteristics of the 108 subjects intubated after HFNC failure are displayed by group in Table 2. The mean age was 60 y, and the majority were male (69.4%) and non-White (87.0%). Most had comorbidities (78.7%), of which the most common were hypertension (48.1%), diabetes mellitus (41.7%), and hyperlipidemia (31.5%). Most clinical characteristics were similar between the 2 groups; however, SOFA score was significantly higher in the early HFNC failure group compared to the late HFNC failure

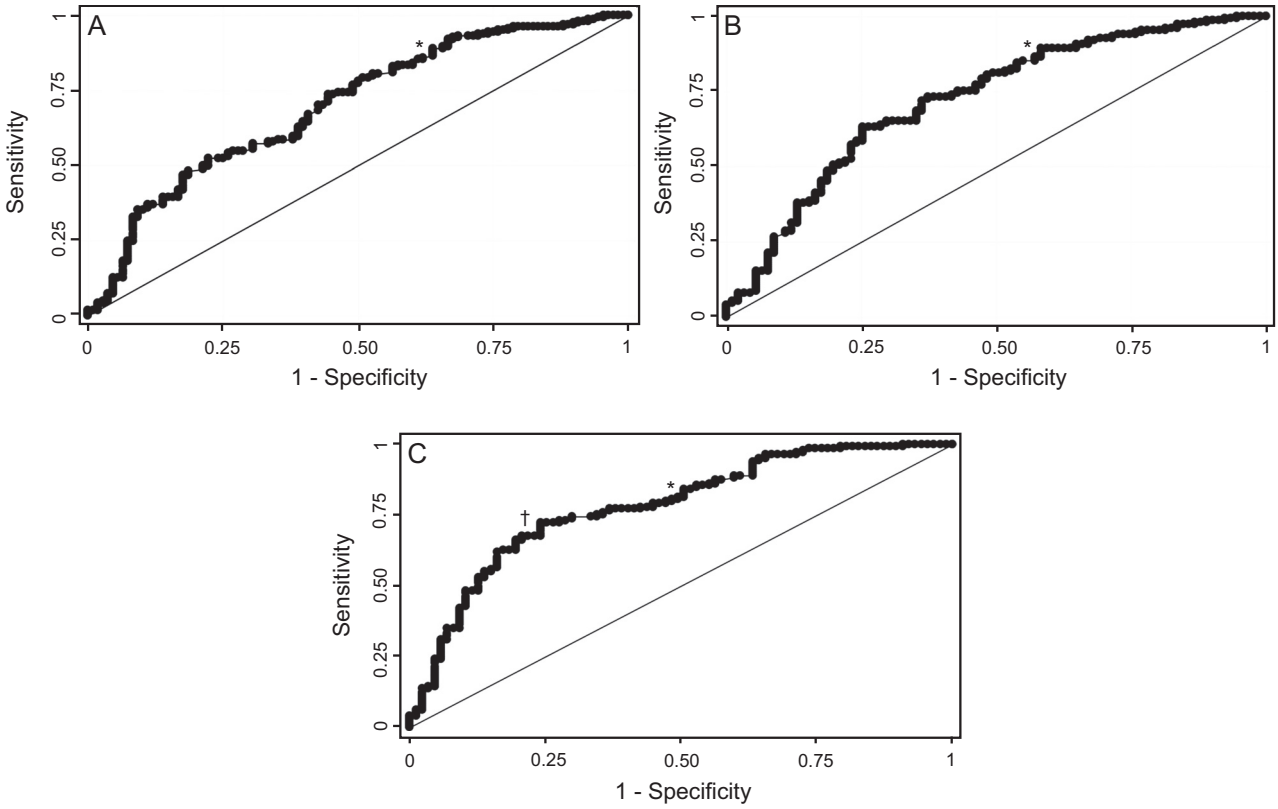

Figure 2. Receiver operator characteristic curves for ROX index at 2 h (A), 6 h (B), and 12 h (C) as predictor of high-flow nasal cannula success. A: Area under the curve (AUC) = 0.70 (CI 0.63–0.76). * ROX index > 3.41, 83.5% sensitivity, 42.6% specificity, positive predictive value (PPV) 68.8%, negative predictive value (NPV) 63.0%. B: AUC = 0.72 (CI 0.65–0.79). * ROX index > 3.46, 89.3.% sensitivity, 41.8% specificity, PPV 69.9%, NPV 71.4% C: AUC = 0.78 (CI 0.72–0.84). C: AUC = 0.78 (CI 0.72–0.84). * ROX index > 3.67, 84.1.% sensitivity, 49.4% specificity, PPV 71.5%, NPV 57.1% † ROX index > 4.57, 72.4% sensitivity, 75.9% specificty, PPV 82.1%, NPV 64.6%.

group. Additionally, subjects who failed HFNC late were more likely to have received adjuvant therapies such as self-proning (39.3% vs 72.3%, $P < .001$), inhaled nitric oxide (14.8% vs 42.6%, $P < .002$), remdesivir (19.7% vs 40.4%, $P = .031$), and systemic steroids (27.9% vs 53.2%, $P = .01$) prior to intubation compared to those intubated after early HFNC failure.

Clinical outcomes are summarized in Table 3. Overall hospital mortality for subjects requiring invasive mechanical ventilation was high (45.4%), which did not differ significantly between the early and late failure groups (39.3% vs 53.2%, $P = .18$). Furthermore, mortality at 14 d after initiation of HFNC (24.6% vs 25.5%, $P > .99$), at 14 d after intubation (24.6% vs 34.0%, $P = .29$), at 28 d after initiation of HFNC (34.4% vs 42.6%, $P = .43$), and at 28 d after intubation (34.4% vs 51.1%, $P = .12$) were not significantly different between the groups. ECMO requirements (13.1% vs 14.9%, $P = .79$) and median (IQR) ICU length of stay were also similar (14 d [IQR 9–20] vs 15 d [IQR 8–23], $P = .95$).

Table 4 demonstrates the relationship between clinical factors and overall hospital mortality for subjects intubated after HFNC failure. In univariate regression analysis, significant factors were age, male gender, heart rate, mean arterial pressure, and SOFA score. After adjustment for multiple variables, no significant difference between the primary or secondary end points was noted for either group (Table 5).

Additional ICU complications by early versus late HFNC failure are displayed in Table 6. Notably, pneumothorax, secondary infection, and acute kidney injury were common, occurring in 11.1%, 29.6%, and 55.6% of the study population, respectively. There were no significant differences for any of the complications between the groups.

Discussion

Our study documents the clinical outcomes of 272 subjects with respiratory failure related to COVID-19 that was treated with HFNC. A significant portion (60.3%) of subjects with respiratory failure related to COVID-19 were managed successfully with HFNC and never required initiation of mechanical ventilation. Strikingly, 111 (67.7%) of these subjects were managed successfully in non-ICU settings. Of the 108 subjects treated with HFNC who ultimately required

Table 2. Baseline Characteristics of Subjects Intubated After HFNC Failure

	All Subjects ($n = 108$)	Early HFNC Failure ($n = 61$)	Late HFNC Failure ($n = 47$)	P
Age, y	60 ± 13	58 ± 13	62 ± 11	.07
Female	33 (3.6)	18 (29.5)	15 (31.9)	.84
Race, non-White	94 (87.0)	55 (9.2)	39 (83.0)	.39
Body mass index, kg/m^2	28.7 (24.9–33.6)	3.2 (26.3–35.7)	27.9 (23.5–32.9)	.08
HFNC duration, d	2 (1, 4)	1 (0, 1)	4 (3, 8)	< .001
Comorbid diseases				
No comorbid disease	23 (21.3)	17 (27.9)	6 (12.8)	.063
Hypertension	52 (48.1)	25 (41.0)	27 (57.4)	.12
Diabetes mellitus	45 (41.7)	23 (37.7)	22 (46.8)	.43
Chronic kidney disease	12 (11.1)	7 (11.5)	5 (1.6)	> .99
End-stage renal disease	4 (3.7)	3 (4.9)	1 (2.1)	.63
Coronary artery disease	4 (3.7)	2 (3.3)	2 (4.3)	> .99
Hyperlipidemia	34 (31.5)	16 (26.2)	18 (38.3)	.21
Asthma	4 (3.7)	2 (3.3)	2 (4.3)	> .99
COPD	1 (.9)	1 (1.6)	0 (0)	> .99
Active cancer	6 (5.6)	5 (8.2)	1 (2.1)	.23
HFrEF	2 (1.9)	0 (0)	2 (4.3)	.19
Systemic anticoagulation	1 (.9)	1 (1.6)	0 (0)	> .99
Clinical data at HFNC initiation				
Heart rate, beats/min	95 (82–104)	99 (85–104)	93 (80–100)	.22
Mean arterial pressure, mm Hg	9.3 ± 13.2	90.4 ± 13.6	9.1 ± 12.9	.91
Breathing frequency, breaths/min	30 (26–37)	30 (25.5–37)	31 (26–37)	.65
Oxygen saturation	93 (89–95)	93 (88–94)	93 (90–96)	.42
SOFA score	4 (2–7)	5 (2–8)	4 (2–5)	.02
White blood cells, $\times 10^9$ per mL	8.9 (6.1–11.6)	9.2 (6.1–11.5)	8.4 (6.1–11.9)	.93
Neutrophil to lymphocyte ratio	8.1 (4.9–12.0)	9.0 (4.3–12.9)	7.4 (5.6–11.6)	.80
Lactate, mmol/L	1.9 (1.4–2.8)	1.8 (1.3–2.8)	2.0 (1.5–3.0)	.41
C-reactive protein, mg/L	17.2 (1.8–26.3)	18.0 (11.1–28.2)	16.7 (9.7–23.3)	.47
D-dimer, μg/mL	1.3 (0.9–2.7)	1.5 (0.9–2.5)	1.2 (0.8–2.9)	.97
Procalcitonin, ng/mL	0.3 (0.1–1.0)	0.3 (0.1–1.2)	0.3 (0.1–0.6)	.13
Adjunctive measures prior to intubation				
Self-proning	58 (53.7)	24 (39.3)	34 (72.3)	< .001
Inhaled nitric oxide	29 (26.9)	9 (14.8)	20 (42.6)	< .002
Remdesivir	31 (28.7)	12 (19.7)	19 (40.4)	.031
Systemic steroids	42 (38.9)	17 (27.9)	25 (53.2)	.01

Data presented as mean ± SD, median (interquartile range), or n (%) unless otherwise indicated.
HFNC = high-flow nasal cannula
HFrEF = heart failure with reduced ejection fraction
SOFA = Sequential Organ Failure Assessment

endotracheal intubation, we noted high overall mortality (45.4%), significant use of ECMO (13.9%), and a longer median stay in the ICU of 14 d (IQR 8–21).

HFNC has previously been reported to have several positive physiologic and clinical advantages in the treatment of acute respiratory failure. HFNC can enhance patient comfort through a reduction of important subjective patient-reported symptoms, including dyspnea and oral dryness, compared to conventional oxygen delivery.[4] Additionally, HFNC may provide physiologic benefit from a reduction in patient work of breathing and a decrease in physiologic dead space though high air flows.[19] HFNC has been used successfully in the management of respiratory distress related to other viral illnesses, and data suggest that the use of HFNC in COVID-19 has the potential to decrease the need for mechanical ventilation.[6,20] Avoidance of intubation may allow for a reduction in complications commonly associated with endotracheal intubation such as pneumonia, ventilator-associated lung injury, or secondary infections. Furthermore, avoidance of mechanical ventilation through the use of HFNC may help conserve this valuable resource in the event of ventilator shortages.

However, despite these advantages, there is concern that poor patient selection or prolonged trials of HFNC may

Table 3. Primary and Secondary Outcomes of Subjects Intubated After HFNC Failure

	All Subjects (n =108)	Early HFNC Failure (n = 61)	Late HFNC Failure (n = 47)	P
Primary outcome				
Overall hospital mortality	49 (45.4)	24 (39.3)	25 (53.2)	.18
Secondary outcomes				
Progression to ECMO	15 (13.9)	8 (13.1)	7 (14.9)	.79
Mortality at 14 days following HFNC	27 (25.0)	15 (24.6)	12 (25.5)	> .99
Mortality at 14 days following intubation	31 (28.7)	15 (24.6)	16 (34.0)	.29
Mortality at 28 days following HFNC	41 (38.0)	21 (34.4)	20 (42.6)	.43
Mortality at 28 days following intubation	45 (41.7)	21 (34.4)	24 (51.1)	.12
ICU length of stay, d	14 (8–21)	14 (9–20)	15 (8–23)	.95

Data presented as n (%) or median (interquartile range).
HFNC = high-flow nasal cannula
ECMO = extracorporeal membrane oxygenation

Table 4. Factors Associated With Overall In-Hospital Mortality in Subjects Intubated After HFNC Failure

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Age	1.11 (1.05–1.14)	< .001	1.10 (1.05–1.16)	< .001
Male	2.49 (1.04–5.95)	.040	2.40 (0.81–7.10)	.11
Race, non-White	1.12 (0.36–3.49)	.84		
Body mass index, kg/m^2	1.00 (0.95–1.05)	.98		
Comorbidities				
Hypertension	1.43 (0.67–3.07)	.35		
Diabetes mellitus	1.09 (0.51–2.36)	.82		
Chronic kidney disease	1.23 (0.37–4.10)	.73		
Coronary artery disease	3.78 (0.38–37.58)	.26		
Hyperlipidemia	1.10 (0.49–2.49)	.81		
Obstructive lung disease	0.79 (0.13–4.96)	.81		
Active cancer	6.59 (0.74–58.45)	.09		
HFrEF	1.21 (0.07–19.83)	.90		
Clinical data prior to HFNC initiation				
Heart rate, per 10 beats/min	1.34 (1.04–1.63)	.02	1.63 (1.10–2.16)	< .001
Mean arterial pressure, per 10 mm Hg	1.34 (1.10–1.97)	.049		
Breathing frequency, breaths/min	1.01 (0.97–1.06)	.55		
Oxygen saturation	0.99 (0.94–1.04)	.69		
SOFA score	1.12 (1.00–1.25)	.049		
White blood cells,	1.04 (0.95–1.13)	.42		
Neutrophil to lymphocyte ratio	1.01 (0.98–1.05)	.56		
Lactate	1.33 (0.96–1.83)	.08		
C-reactive protein	1.00 (0.97–1.03)	.98		
D-dimer	1.06 (0.96–1.19)	.26		
Procalcitonin	1.01 (0.99–1.03)	.38		
Adjunctive measures prior to intubation				
Self-proning	0.71 (0.33–1.51)	.37		
Inhaled nitric oxide	0.80 (0.34–1.90)	.61		
Remdesivir	1.19 (0.51–2.73)	.69		
Systemic steroids	1.59 (0.73–3.46)	.24		

HFNC = high-flow nasal cannula
HFrEF = heart failure with reduced ejection fraction
SOFA = sequential organ failure assessment

Table 5. Outcomes of Subjects Intubated After HFNC Failure With Adjustment for Confounders

	Unadjusted Odds Ratio (95% CI)	P*	Adjusted Odds Ratio (95% CI)	P*
Primary outcome				
Overall hospital mortality	1.75 (0.81–3.78)	.15	2.13 (0.80–5.62)	.13
Secondary outcomes				
Progression to ECMO	1.16 (0.39–3.46)	.79	1.78 (0.43–7.32)	.42
Mortality at 14 d after HFNC	1.05 (0.44–2.53)	.91	0.97 (0.35–2.69)	.95
Mortality at 14 d after intubation	1.58 (0.68–3.66)	.28	1.45 (0.53–3.96)	.46
Mortality at 28 d after HFNC	1.41 (0.64–3.09)	.39	1.39 (0.51–3.81)	.52
Mortality at 28 d after intubation	1.99 (0.91–4.33)	.08	2.53 (0.91–7.00)	.07
ICU length of stay	0.95 (0.72–1.26)†	.73‡	0.92 (0.71–1.18)†	.50‡

Early failure was used as the reference for comparison.
* Statistical comparison of the data were performed using logistic regression analysis.
† Relative ratio by negative binomial regression analysis.
‡ Statistical comparison performed using negative binomial regression analysis.
HFNC = high-flow nasal cannula
ECMO = extracorporeal membrane oxygenation

Table 6. Complications During ICU Stay of Subjects by Early Versus Late HFNC Failure

	All Subjects (n = 108)	Early HFNC Failure (n = 61)	Late HFNC Failure (n = 47)	P
Pneumothorax	12 (11.1)	6 (9.8)	6 (12.8)	.76
VAP	19 (17.6)	10 (16.4)	9 (19.1)	.80
Secondary infection	32 (29.6)	16 (26.2)	16 (34.0)	.40
Acute kidney injury	60 (55.6)	32 (52.5)	28 (59.6)	.56
Need for renal replacement therapy	29 (26.9)	20 (32.8)	9 (19.1)	.13
Venous thromboembolism	12 (11.1)	8 (13.1)	4 (8.5)	.55

Data are presented as *n* (%).
HFNC = high-flow nasal cannula
VAP = ventilator-associated pneumonia

result in worse clinical outcomes. In an observational study prior to the emergence of SARS-CoV-2, delayed failure of HFNC was associated with worse overall ICU mortality and fewer ventilator-free days at day 28.[21] However, it is not clear how these prior data translate to the unique clinical syndrome of COVID-19.

The use of HFNC in the treatment of COVID-19 has become common, with multiple case series reporting high proportions of critically ill subjects receiving this therapy.[13,22] Despite this, controversy exists regarding the timing of progression from HFNC to mechanical ventilation should patients fail to wean from HFNC or their clinical condition worsen. Some have argued that vigorous spontaneous inspiratory efforts can lead to volutrauma and self-induced lung injury after large swings in transpulmonary pressure and associated lung stress. Therefore, in some instances, experts have advocated that intubation should be performed as soon as possible.[12] It has been further suggested that, given the prolonged duration of COVID-19 illness, the use of noninvasive ventilation may have an unacceptably high failure rate and may delay endotracheal intubation.[14] However, others have argued that the liberal use of early mechanical ventilation for the respiratory failure associated with COVID-19 is not justified. This latter argument has led some clinicians to consider prolonged trials of HFNC in an effort to avoid endotracheal intubation and its associated complications.[15,16]

Our study provides evidence that prolonged trials of HFNC in patients with respiratory failure related to COVID-19 may be reasonable and are not clearly associated with adverse clinical patient outcomes. We failed to demonstrate any difference in our primary end point (ie, overall hospital mortality) or any of the secondary end points including the need for ECMO, mortality at 14 d and 28 d after HFNC and endotracheal intubation, and ICU length of stay. Despite these findings, we recognize that the decision regarding the optimal strategy and timing of intubation is nuanced and patient-specific. Poor patient selection, lack of appropriate monitoring, and failure to recognize clinical deterioration in patients on HFNC are likely to be related to adverse clinical outcomes.

Our results further suggest that, as in other causes of hypoxemic respiratory failure, the ROX index has a high sensitivity in identifying patients likely to succeed on HFNC. It may help select patients who could benefit from HFNC and those who could safely undergo prolonged trials of HFNC as a means of avoiding intubation in respiratory failure related to COVID-19. The ROX index was first described and validated in subjects with respiratory failure prior to the outbreak of COVID-19. This index has also been applied to predict the need for endotracheal intubation after HFNC application in subjects with COVID-19. However, unlike our current analysis, most other research has emphasized the identification of patients likely to ultimately fail HFNC.[8-10] In a previous cohort of subjects with COVID-19,[11] in which the ROX index was applied to predict successful weaning from HFNC, the authors described similar model accuracy. In the analysis of this cohort, a ROX index cutoff was identified at a single time interval (ie, 4 h) following the application of HFNC. Our results build on this earlier work by applying the ROX index at multiple time intervals after the application of HFNC and demonstrating that monitoring the ROX index over time may aid in the identification of patients who can ultimately be weaned from HFNC. Given the similarity in clinical outcomes between early and late failure subjects in our cohort, prediction of HFNC success may be of clinical utility. Our results indicate that the index appears to perform similarly in respiratory failure related to COVID-19 compared to the non-COVID-19 cohort in which it was initially evaluated. We identified ROX index cutoffs that may be useful in selecting patients who could be successfully weaned from HFNC without the need for endotracheal intubation.

Subjects in the early failure group were more likely to have a higher overall illness severity, but the magnitude of this difference was small and may not be clinically important. Though most of the baseline clinical characteristics were otherwise similar between the groups, subjects with late HFNC failure were more likely to have received adjunctive therapies such as self-proning, inhaled vasodilators, remdesivir, and steroids prior to endotracheal intubation. We postulate this may reflect additional therapies trialed by clinicians in an effort to stave off mechanical ventilation, and we acknowledge that this treatment difference may confound outcome differences between the groups. In univariate analysis, these therapies were not significantly associated with mortality in this small sample size. Of note, no health care workers in the Inova Health System were suspected of iatrogenic infection with COVID-19 during the study period, which is likely a testament to the safety of HFNC in this setting, staff diligence, and the efficacy of appropriate personal protective equipment utilized per clinical practice guidelines.

This analysis has several limitations. First, this was a retrospective observational study. Though attempts were made to correct for covariates, all confounders may not have been accounted for and likely cannot be in the absence of a randomized clinical trial. Second, this trial was performed within a single hospital system. Heterogeneity in practice patterns is likely, and similar data from multiple hospital systems would be informative. Additionally, given the small size of our study population, it is feasible our study lacked the statistical power to detect differences in clinical outcomes between the groups. Finally, although the ROX index is well suited for application in clinical care, given the ability to rapidly calculate it at the bedside on the basis of universally available clinical data, other prediction models may be more accurate or even easier to apply in clinical practice. Efforts to validate additional predictors or combinations of predictors to identify patients with COVID-19 likely to be weaned from noninvasive ventilation is a continued area of interest and deserves future research. Prospective trials with larger sample sizes are required to further explore these important clinical questions.

Conclusions

Respiratory failure related to COVID-19 is a unique condition for which strategies regarding noninvasive and invasive ventilation management are still being optimized. In this retrospective review, we noted that HFNC was utilized frequently, and many subjects with hypoxemic respiratory failure related to COVID-19 did not require intubation after management with this therapy. Prolonged use of HFNC was not associated with worse clinical outcomes compared with shorter trials in those who ultimately required mechanical ventilation. The ROX index was sensitive for the identification of subjects who were successfully managed with HFNC without the subsequent need for endotracheal intubation. A ROX index > 3.67 at 12 h after the application of HFNC was an accurate predictor of successful weaning in our cohort. Prospective study of HFNC in COVID-19 is warranted to confirm these findings and to optimize patient selection for use of this device in this evolving care setting.

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