Inhaled Nitric Oxide via High-Flow Nasal Cannula in Patients with Acute Respiratory Failure Related to COVID-19

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ABSTRACT

INTRODUCTION: Limited evidence exists regarding use of inhaled nitric oxide (iNO) in spontaneously breathing patients. We evaluated the effectiveness of continuous iNO via high-flow nasal cannula (HFNC) in COVID-19 respiratory failure.

METHODS: We performed a multicenter cohort study of patients with respiratory failure from COVID-19 managed with HFNC. Patients were stratified by administration of iNO via HFNC. Regression analysis was used to compare the need for mechanical ventilation and secondary endpoints including hospital mortality, length of stay, acute kidney injury, need for renal replacement therapy, and need for extracorporeal life support.

RESULTS: A total of 272 patients were identified and 66 (24.3%) of these patients received iNO via HFNC for a median of 88 h (interquartile range: 44, 135). After 12 h of iNO, supplemental oxygen requirement was unchanged or increased in 52.7% of patients. Twenty-nine (43.9%) patients treated with iNO compared to 79 (38.3%) patients without iNO therapy required endotracheal intubation ($P = .47$). After multivariable adjustment, there was no difference in need for mechanical ventilation between groups (odds ratio: 1.53; 95% confidence interval [CI]: 0.74-3.17), however, iNO administration was associated with longer hospital length of stay (incidence rate ratio: 1.41; 95% CI: 1.31-1.51). No difference was found for mortality, acute kidney injury, need for renal replacement therapy, or need for extracorporeal life support.

CONCLUSION: In patients with COVID-19 respiratory failure, iNO delivered via HFNC did not reduce oxygen requirements in the majority of patients or improve clinical outcomes. Given the observed association with increased length of stay, judicious selection of those likely to benefit from this therapy is warranted.

KEYWORDS: COVID-19, high-flow nasal cannula, inhaled nitric oxide, acute respiratory distress syndrome, respiratory failure

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Introduction

Patients with coronavirus disease 2019 (COVID-19) face substantial morbidity and mortality related to viral pneumonitis and subsequent respiratory failure that can progress to acute respiratory distress syndrome (ARDS).[1] Management strategies for acute respiratory failure related to this condition are still evolving and patients with COVID-19 that require mechanical ventilation face a mortality risk of roughly 40%.[2] Given the high mortality rate in patients that ultimately require mechanical ventilation, strategies to avoid early endotracheal intubation in these patients have been commonly employed.[3] High humidity, high-flow nasal cannula (HFNC) devices deliver warmed and humidified oxygen at flow rates up to 60 L/min with a fraction of inspired oxygen up to 100%.[4] This device has been widely utilized in the management of acute respiratory failure in COVID-19 and evidence suggests its use may decrease the need for invasive mechanical ventilation.[3,5] In addition to HFNC, other adjunctive measures have been employed in an effort to "rescue" patients at risk of further decompensation and subsequent endotracheal intubation.[6] One such therapy commonly utilized in this setting is continuous inhaled nitric oxide (iNO).

iNO is a potent vasodilator which can produce vascular and bronchial smooth muscle relaxation.[7] Through the former mechanism, it can cause selective pulmonary vasodilation in well-ventilated lung regions and thereby improve ventilation-perfusion matching and reduce pulmonary vascular resistance.[7] Although iNO has historically been most commonly administered through closed systems in intubated patients or in patients with tight fitting masks, it may also be administered via open systems such as HFNC and similar devices.[8] Though limited data is available related to its use in the treatment of hypoxemia related to COVID-19, high quality evidence exists regarding the use of iNO in mechanically ventilated patients with

ARDS from other causes. This prior evidence suggests that iNO can transiently improve oxygenation, but is not associated with a reduction in ventilator free days, duration of mechanical ventilation, ICU and hospital length of stay, or mortality.[9] Further, the therapy has been demonstrated to be associated with increased risk of renal dysfunction and a previous meta-analysis of available evidence reached the conclusion that iNO should be used in the management of ARDS only as part of future randomized clinical trials.[9,10] Also of interest, the therapy itself may add significantly to the financial cost of ICU care given previous published estimates of cost of therapy of more than $100/h.[11,12]

There has been renewed interest in the utility of iNO as it relates specifically to COVID-19. During the SARS-CoV epidemic in 2004, researchers hypothesized that iNO may not only exert an effect through pulmonary vasodilation, but also possibly through antiviral mediated effects.[13] Similarly, it has been described that nitric oxide concentration and bioavailability of this endogenous molecule is decreased in patients with COVID-19. Thus, investigators have postulated that exogenous administration may help improve clinical outcomes.[14] To date, a number of small pilot studies have investigated the administration of iNO to patients with COVID-19. The majority have noted modest improvement in oxygenation with its administration, but the effect on clinical outcomes when compared to iNO naïve patients remains unknown.[15] While iNO has been extensively evaluated as a rescue therapy in mechanically ventilated patients with ARDS, the effects on patient outcomes in spontaneously breathing patients with hypoxemic respiratory failure due to causes other than COVID-19 are not well described. Notably, a randomized trial of iNO in spontaneously breathing patients with mild to moderate COVID-19 requiring supplemental oxygen was recently placed on hold after interim analysis of data from the first 100 patients.[22] Complete data from this trial is not yet publicly available. In this study, we sought to evaluate the utility of iNO in patients managed with HFNC for the support of COVID-19 associated respiratory failure.

Methods

Patient Population

We performed a multicenter retrospective observational study of patients treated for acute respiratory failure secondary to COVID-19 and managed with HFNC. Data for this analysis was obtained from an existing database for which patients were included if ≥18 years of age, with a laboratory confirmed diagnosis of COVID-19 by polymerase chain reaction testing, and treated with HFNC for ≥2 h. Patients were excluded if endotracheal intubation was performed prior to initiation of HFNC (ie, HFNC was used as a weaning modality from mechanical ventilation), performed on an elective basis (ie, for surgical procedure), or the patient was switched to noninvasive ventilation prior to endotracheal intubation. Patients for whom endotracheal intubation was not within their goals of care were also excluded.

Data was collected for patients admitted to the Inova Health System between March 1, 2020 and June 9, 2020. The Inova Health System consists of 5 hospitals, including a large tertiary care center and 4 community hospitals. The study was approved by the Institutional Review Board (IRB# U20-06-4134) at Inova Fairfax Hospital. All data were collected from the electronic medical record (Epic®).

Inova Health System COVID-19 Management Protocol

The strategy for the management of acute respiratory failure was fairly homogenous across our healthcare system. Efforts were made to avoid intubation where feasible with the use of HFNC. HFNC was provided via the Fisher & Paykel Optiflow™ system. Noninvasive ventilation was largely avoided early on due to concerns regarding aerosolizing the SARS-CoV-2 virus, but was increasingly utilized over time. iNO was delivered in a blend with oxygen via HFNC utilizing the INOmax DS® (Mallinckrodt Pharmaceuticals, USA) system and self-proning was incorporated where deemed clinically appropriate. Patients clinically suitable for self-proning were encouraged to maintain this positioning, as tolerated, for up to 16 h per day. Patients were initiated on iNO via HFNC at the discretion of their attending physician. No clinical conditions were considered a strict contraindication to iNO therapy. Patients were generally started at a dose of 20 parts per million (ppm). If there was no response (as measured by an improvement of 5% in oxygen saturation) after 1 h of therapy, iNO was increased to 40 ppm. If patients again failed to respond after 1 h, iNO was recommended to be discontinued; however, this too was ultimately left at the discretion of the attending physician. If patients responded to iNO, they were weaned to the lowest effective dose. Other adjunct therapeutics targeting COVID-19 disease were also 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. The need for endotracheal intubation after HFNC was generally based on the presence of hypoxemia with a failure to maintain an oxygen saturation >88% despite receiving the maximal fraction of inspired oxygen allowed by the HFNC, respiratory rate >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, patients were typically managed initially with moderate positive end-expiratory pressure (PEEP) (10-12 cm H_2O) and a lung protective ventilator strategy.

Neuromuscular blockade and prone positioning were frequently utilized in patients 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.[23] Patients were considered for extracorporeal membrane oxygenation if age <60 years old, on invasive mechanical ventilation <10 days, and had a PaO_2/FiO_2 ratio <100 and had failed lung protective ventilation despite neuromuscular blockade and prone positioning.

Data Collection

Data was abstracted in a structured format by 3 of the authors (AC, SP, and DS). Data collated included demographics, comorbid diseases (as documented in the admitting history and physical), clinical data (including vital signs, common laboratories, and illness severity as estimated by the sequential organ failure assessment [SOFA] score). Laboratory data was collected when available within 6 h of the initiation of HFNC. Adjunctive measures provided while patients were receiving HFNC, such as the use of prone positioning or the administration of iNO, remdesivir, or systemic steroids (defined as equivalent of prednisone 20 mg daily or greater) were also recorded. Patients in the iNO group received at least 1 h of continuous iNO via HFNC. For patients that received iNO via HFNC, dose, total duration, and the administered fraction of inspired supplemental oxygen was collected at the time of iNO initiation and at 12 h after initiation of this therapy.

The primary outcome examined was the need for mechanical ventilation. Secondary endpoints included overall hospital mortality, hospital length of stay, acute kidney injury (defined a rise in serum creatinine by ≥0.3 mg/dL over 48 h), need for renal replacement therapy, and the need for extracorporeal life support. To explore the effect of possible immortal time bias, a subgroup analysis of the primary and secondary endpoints of patients on HFNC for ≥3 days was performed.

To further investigate characteristics of patients most likely to benefit from iNO delivered via HFNC, patients that received this medication were classified as responders (defined as a decrease in supplemental oxygen delivered via HFNC 12 h after initiation of iNO) or as nonresponders (no change or increase in supplemental oxygen delivered). Patient factors associated with treatment response and the effect of treatment response on subsequent need for mechanical ventilation were then examined.

Statistics

Distribution of all continuous data was examined for normality using visual inspection and the Wilk Shapiro test. Characteristics of the groups are presented using the mean and standard deviation for normally distributed data and compared between groups using the 2 sample *t*-test. Data not normally distributed are presented as median and interquartile range (IQR) and compared using the Wilcoxon rank sum test. Categorical data are presented as counts with proportions and compared using Fisher's exact test (2-tailed). In order to compare clinical outcomes between patients managed with standard HFNC and those managed with HFNC and iNO, we performed logistic regression analysis to model the need for mechanical ventilation, hospital mortality, acute kidney injury, need for renal replacement therapy, and need for extracorporeal life support. Hospital length of stay demonstrated a positively skewed distribution. To minimize the effects of outliers and to account for this distribution, Poisson regression was selected and utilized to compare this outcome. Results of logistic regression are described using the odds ratio (OR) together with the 95% confidence interval (95% CI), whereas results of the Poisson regression model are described using an incidence rate ratio (IRR). A P value <.05 was considered statistically significant. Univariate and multivariable logistic regression analysis of factors possibly associated with mortality were performed. Variables were dropped from the model through use of the likelihood ratio test. All statistical analyses were performed using STATA version 14 (StataCorp LP).

Results

Characteristics of the Cohort

During the study period, our search strategy identified 393 patients with respiratory failure secondary to COVID-19 that required the use of HFNC within the Inova Health System. Patients that did not receive HFNC therapy prior to endotracheal intubation ($N=27$), were switched to noninvasive positive pressure ventilation ($N=21$), were intubated for an elective reason ($N=1$), or were <18 years of age ($N=6$) were excluded from data collection. Given the primary study objective was to analyze the effect of management strategy on the subsequent need for mechanical ventilation; 66 patients were excluded as intubation and mechanical ventilation did not align with their goals of care. Of the remaining 272 patients, 66 (24.3%) patients received continuous iNO via the HFNC device (Figure 1). Outcome data was available for all patients at the time of data analysis.

The characteristics of the 272 patients managed with HFNC stratified by administration of iNO are presented in Table 1. Average age was 57 ± 13 years, 92 (33.8%) patients were women, and the majority of patients (91.2%) were nonwhite. Compared to those that did not receive iNO, patients that received this therapy were less likely to have baseline medical comorbidities, had lower initial oxygen saturation at the time of HFNC application, and also remained on HFNC for longer compared to patients that did not receive this therapy. iNO recipients were less likely to have undergone self-proning, but were more likely to have received other adjuvant therapies (such as remdesivir, systemic steroids, targeted

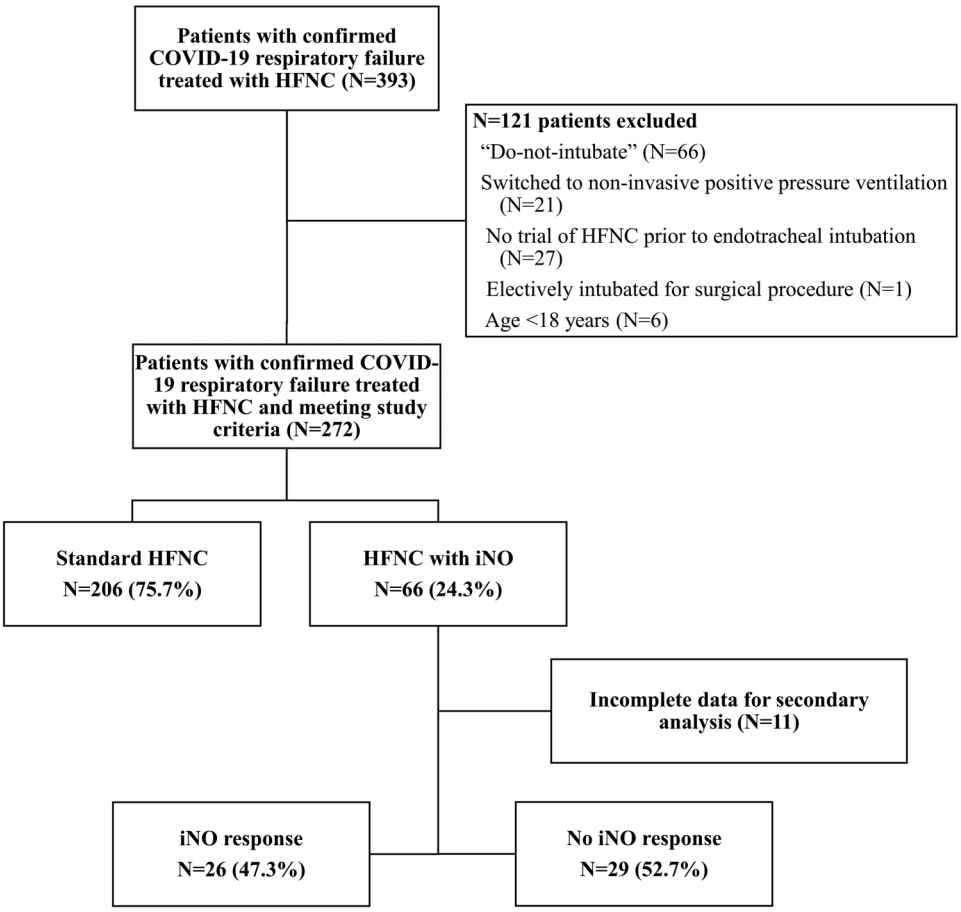

Figure 1. Flowchart of patients with COVID-19 associated respiratory failure treated with high-flow nasal cannula (HFNC) in the Inova Health System between March 1, 2020 and June 9, 2020.

immunomodulators, and convalescent plasma) for the management of COVID-19 while receiving HFNC.

Clinical Outcomes

The unadjusted clinical outcomes of the cohort are included in Table 2. Overall, 108 (39.7%) patients required endotracheal intubation and 48 (17.6%) of the patients died during hospitalization. There was no difference between patients that received HFNC alone compared with those that received iNO via HFNC for the primary endpoint of need for subsequent mechanical ventilation (38.3% vs 43.9%; $P = .470$). Of the secondary endpoints, a significant difference was noted between the groups in the occurrence of acute kidney injury and hospital length of stay. Fewer patients in the HFNC with iNO group developed acute kidney injury (33.5% vs 19.7%; $P = .044$). However, hospital length of stay was significantly longer (13 vs 17.5 days; $P < .001$) in patients that received iNO. No significant differences were noted in the need for renal replacement therapy, need for extracorporeal life support, or death during hospitalization. Notably, a methemoglobin value >5% was not detected in any patient during the study period.

Table 3 demonstrates the relationship between clinical factors and overall hospital mortality for patients in the cohort. In univariate regression analysis, factors significantly associated with increased mortality included age, male gender, history of cancer, heart rate at time of HFNC application, SOFA score, and serum lactate concentration. Patient self-proning and the administration of systemic steroids were associated with decreased mortality. The final multivariable model included age, gender, heart rate at time of HFNC application, and SOFA score. Based on the likelihood ratio test, the inclusion of the variables history of cancer, serum lactate concentration, and systemic steroids did not add significant accuracy to the model and were dropped. After multivariable adjustment, there continued to be no difference in the need for mechanical ventilation between patients that received iNO compared to those that did not (OR: 1.53; 95% CI: 0.74-3.17) (Table 4). Further, after adjusting for covariates, no statistical difference in risk of acute kidney injury was found between groups (OR: 0.48; 95% CI: 0.21-1.06). However, hospital length of stay remained significantly longer among patients that received continuous iNO via HFNC (IRR: 1.41; 95% CI: 1.31-1.51). To explore the potential effect of immortal time bias, a subgroup

Table 1. Baseline Characteristics of Patients Stratified by Administration of Inhaled Nitric Oxide.

	All subjects	Standard HFNC	HFNC with iNO	
	N = 272	*N* = 206	*N* = 66	*P* value
Age (years)	57 ± 13	56 ± 14	57 ± 13	.699
Gender, women	92 (33.8)	71 (34.5)	21 (31.8)	.766
Race, nonwhite	248 (91.2)	185 (89.8)	63 (95.5)	.214
Body mass index (kg/m^2)	28.7 (25.2, 33.4)	28.7 (25.8, 33.7)	27.8 (24.3, 32.4)	.239
HFNC treatment time (days)	3 (1, 6)	3 (1, 5)	6 (3, 8)	<.001
Comorbid diseases				
No known comorbid disease	83 (30.5)	56 (27.2)	27 (40.9)	.045
Hypertension	116 (42.6)	96 (46.6)	20 (30.3)	.022
Diabetes mellitus	101 (37.1)	75 (36.4)	26 (39.4)	.663
Chronic kidney disease	20 (7.4)	18 (8.7)	2 (3.0)	.175
End-stage renal disease	8 (2.9)	6 (2.9)	2 (3.0)	.999
Coronary artery disease	9 (3.3)	8 (3.9)	1 (1.5)	.692
Hyperlipidemia	74 (27.2)	60 (29.1)	14 (21.2)	.266
Asthma	13 (4.8)	11 (5.3)	2 (3.0)	.740
COPD	2 (0.7)	2 (1.0)	0 (0)	.999
Active cancer	7 (2.6)	7 (3.4)	0 (0)	.201
HFrEF	4 (1.5)	3 (1.5)	1 (1.5)	.999
Systemic anticoagulation	9 (3.3)	6 (2.9)	3 (4.5)	.457
Clinical data at time of initiation of HFNC				
Heart rate (bpm)	93 (80, 104)	93 (80, 103)	92 (80, 105)	.981
Mean arterial pressure (mm Hg)	89.7 ± 13.0	89.1 ± 13.3	91.8 ± 12.1	.171
Respiratory rate (per min)	29 (24, 36)	29 (24, 36)	30 (26, 37)	.174
Oxygen saturation	93 (90, 96)	93 (90, 96)	92 (88, 95)	.028
SOFA score	3 (1, 5)	3 (1, 5)	3 (1, 4)	.302
WBC (×10^9/mL)	8.3 (6.0, 11.4)	8.4 (5.9, 10.9)	8.3 (6.1, 12.0)	.479
NLR ratio	6.5 (4.2, 11.7)	6.5 (4.2, 11.8)	6.5 (4.9, 11.2)	.937
Lactate (mmol/L)	1.7 (1.3, 2.3)	1.7 (1.3, 2.2)	1.9 (1.5, 2.4)	.119
CRP (mg/L)	16.8 (10.0, 24.2)	16.1 (9.7, 23.6)	20.0 (12.4, 27.3)	.041
D-dimer (μg/mL)	1.3 (0.9, 2.5)	1.3 (0.9, 2.2)	1.3 (0.8, 2.7)	.402
Procalcitonin (ng/mL)	0.3 (0.1, 0.6)	0.3 (0.1, 0.6)	0.2 (0.1, 0.4)	.067
Adjunctive treatment measures				
Self-proning	77 (28.3)	71 (34.5)	6 (9.1)	<.001
Remdesivir	105 (38.6)	64 (31.1)	41 (62.1)	<.001

(continued)

Table 1. Continued.

	All subjects	Standard HFNC	HFNC with iNO	
	N = 272	*N* = 206	*N* = 66	*P* value
Systemic steroids	167 (61.4)	118 (57.3)	49 (74.2)	.014
Targeted immunomodulator	95 (34.9)	60 (29.1)	35 (53.0)	.001
Convalescent plasma	18 (6.6)	7 (3.4)	11 (16.7)	.001
Antibiotics	255 (93.8)	193 (93.7)	62 (93.9)	.999

Data presented as mean ± standard deviation, median (25th percentile, 75th percentile), or *n* (%) unless otherwise indicated.
Abbreviations: HFNC, high-flow nasal cannula; iNO, inhaled nitric oxide; COPD, chronic obstructive pulmonary disease; HFrEF, heart failure with reduced ejection fraction; SOFA, sequential organ failure assessment; WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio; CRP, c-reactive protein.

analysis excluding patients managed with HFNC for <3 days was performed. In the 157 patients maintained on HFNC for ≥3 days, treatment outcomes were similar to those noted in the primary analysis (Table 5).

Responders Versus Nonresponders

Among the patients that received iNO via HFNC, 11 individuals had incomplete documentation of applied supplemental oxygen at 12 h after initiation of HFNC and were removed from further analysis. Of the remaining 55 patients, the median duration of continuous iNO administration was 88 h (IQR: 91) and standard dosages ranged from 20 to 40 (ppm). Most patients were started on a continuous infusion of 20 ppm or less (*N* = 43), while 12 patients were started at a dose of 40 ppm. No patient in the cohort received iNO at a dose greater than 40 ppm. After 12 h of continuous iNO, supplemental oxygen requirement was unchanged (*N* = 22) or increased (*N* = 7) in 52.7% of patients while 47.3% of patients (*N* = 26) had an improvement in supplemental oxygen requirements (Figure 2).

Patients that had a reduction in supplemental oxygen requirements from baseline to 12 h after initiation of therapy were categorized as responders and their baseline characteristics compared to nonresponders are displayed in Table 6. Higher initial dose of iNO and higher d-dimer concentration were both found to be associated with treatment response in univariate analysis. Total duration of iNO administration was not significantly different between nonresponders and responders (95 h [IQR: 77] vs 92.5 h [IQR: 131]; *P* = .946). Further, there was no difference in the subsequent need for endotracheal intubation among nonresponders versus responders (51.7% vs 30.8%; *P* = .172).

Discussion

In this study, we sought to investigate the outcomes of administration of continuous iNO via HFNC to patients with COVID-19 related respiratory failure. We found rescue administration of iNO in the cohort was common and was delivered via HFNC to 24.3% of patients. Despite common usage, we did not observe any difference in our primary endpoint of need for mechanical ventilation. Further, other

Table 2. Primary and Secondary Outcomes of Patients Intubated After HFNC Failure.

	All subjects	Standard HFNC	HFNC with iNO	*P* value
Primary outcome				
Need for intubation	108 (39.7)	79 (38.3)	29 (43.9)	.470
Secondary outcomes				
Acute kidney injury	82 (30.1)	69 (33.5)	13 (19.7)	.044
Need for renal replacement therapy	46 (16.9)	33 (16.0)	13 (19.7)	.571
Need for ECMO	15 (5.5)	10 (4.9)	5 (7.6)	.369
Hospital length of stay (days)	14 (10, 21)	13 (10, 19.5)	17.5 (12, 32)	<.001
Death during hospitalization	48 (17.6)	36 (17.5)	12 (18.2)	.855

Data presented as mean ± standard deviation, median (25th percentile, 75th percentile), or *n*(%) unless otherwise indicated.
Abbreviations: HFNC, high-flow nasal cannula; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation.

Table 3. Univariate and Multivariate Analysis to Identify Factors Associated With Overall in Hospital Mortality.

	Univariate analysis		Multivariate analysis	
Variables	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age	1.09 (1.06-1.12)	<.001	1.08 (1.04-1.13)	<.001
Male gender	2.19 (1.04-4.64)	.039	2.94 (1.12-7.75)	.029
Race, nonwhite	0.61 (0.23-1.63)	.326		
Body mass index	1.00 (0.96-1.05)	.942		
Comorbidities				
Hypertension	1.76 (0.94-3.30)	.078		
Diabetes mellitus	1.40 (0.74-2.63)	.297		
Chronic kidney disease	2.13 (0.78-5.90)	.140		
Coronary artery disease	2.42 (0.58-10.05)	.223		
Hyperlipidemia	1.43 (0.73-2.80)	.295		
Obstructive lung disease	0.71 (0.15-3.23)	.654		
Active cancer	12.91 (2.42-68.70)	.003		
HFrEF	1.57 (0.16-15.40)	.700		
Clinical data prior to initiation of HFNC				
Heart rate (per 10 bpm)	1.24 (1.06-1.46)	.009	1.30 (1.05-1.61)	.018
Mean arterial pressure (per 10 mm Hg)	1.26 (0.98-1.62)	.073		
Respiratory rate	1.02 (0.98-1.06)	.267		
Oxygen saturation	0.98 (0.95-1.02)	.405		
SOFA score	1.30 (1.17-1.45)	<.001	1.20 (1.04-1.38)	.012
WBC	1.04 (0.97-1.11)	.285		
NLR ratio	1.01 (0.99-1.03)	.345		
Lactate	1.57 (1.20-2.05)	.001		
CRP	1.01 (0.98-1.04)	.640		
D-dimer	1.08 (1.00-1.16)	.055		
Procalcitonin	1.01 (1.00-1.02)	.136		
Adjunctive treatment measures				
Self-proning	0.28 (0.15-0.53)	<.001	0.35 (0.14-0.86)	.021
Remdesivir	0.60 (0.31-1.18)	.142		
Systemic steroids	0.42 (0.22-0.78)	.007		
Targeted immunomodulator	0.73 (0.37-1.43)	.358		
Convalescent plasma	1.36 (0.43-4.34)	.600		
Antibiotics	3.62 (0.47-27.94)	.218		

Abbreviations: HFNC, high-flow nasal cannula; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; SOFA, sequential organ failure assessment; WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio.

important clinical outcomes including the need for renal replacement therapy, need for extracorporeal life support, or death during hospitalization were not significantly associated with the use of iNO in this setting. Administration of iNO was associated with a reduced rate of acute kidney injury in univariate analysis, however, this association was not observed after

Table 4. Analysis of Outcomes of Patients Stratified by Use of Inhaled Nitric Oxide (Standard HFNC as Reference) With Adjustment for Confounders.

	Unadjusted odds ratio (95% CI)	*P* value[a]	Adjusted odds ratio (95% CI)	*P* value[a]
Primary outcome				
Need for intubation	1.26 (0.72–2.21)	.420	1.53 (0.74-3.17)	.257
Secondary outcomes				
Acute kidney injury	0.49 (0.25-0.95)	.036	0.48 (0.21-1.06)	.068
Need for renal replacement therapy	1.29 (0.63-2.62)	.489	1.85 (0.81-4.19)	.144
Need for ECMO	1.61 (0.53-4.88)	.403	2.22 (0.55-8.96)	.261
Hospital length of stay (days)	1.56 (1.47-1.66)[b]	<.001[c]	1.41 (1.31-1.51)[b]	<.001[c]
Death during hospitalization	1.05 (0.51-2.16)	.896	1.74 (0.68-4.47)	.250

Abbreviations: HFNC, high flow nasal cannula; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.
[a]Statistical comparison of the data were performed using logistic regression analysis unless otherwise noted.
[b]Incident rate ratio by Poisson regression analysis.
[c]Statistical comparison performed using Poisson regression analysis.

multivariable adjustment. Interestingly, patients administered iNO were observed to have a longer hospital length of stay compared to patients not given this rescue therapy.

Overall, iNO was associated with a reduction in supplemental oxygen requirement at 12 h after initiation in some patients. However, more than half of the patients who received this therapy had either stable or increasing oxygen requirements after 12 h of therapy. When evaluating the subset of patients considered responders, there was a trend towards decreased need for mechanical ventilation compared to nonresponders. Interestingly, possibly due to clinician preference or difficulty assessing for clinical improvement, the rate of discontinuation in "nonresponders" in our cohort was low.

Given the observed mixed response, we sought to evaluate patient factors associated with improved oxygenation. Higher initial dose of iNO and higher d-dimer concentration were associated with treatment response. Venous thromboembolism and pulmonary microthrombosis have been found to be common feature of severe COVID-19 infection and marked d-dimer elevation is a well-described phenomenon. As in other conditions, this elevation in d-dimer concentration has been associated with increased illness severity and a higher incidence of thrombotic events.[24] Pulmonary vasodilators, such as iNO, may be administered to patients with pulmonary embolism given the potential to improve right ventricular function and ventilation-perfusion matching.[25] Possibly, the association with higher d-dimer concentration in patients that responded to iNO may reflect a higher rate of macrothrombosis or microthrombosis in this group and an associated response to therapy as a result of this secondary condition. However, given the small sample size and multiple statistical comparisons, this association should be interpreted cautiously. Notably, none of the patients in this cohort had known pulmonary arterial hypertension at baseline and most patients did not have a history of

Table 5. Subgroup Analysis of Outcomes of Patients on HFNC Greater Than 2 days Stratified by Use of Inhaled Nitric Oxide (Standard HFNC as Reference) With Adjustment for Confounders.

	Unadjusted odds ratio (95% CI)	*P* value[a]	Adjusted odds ratio (95% CI)	*P* value[a]
Primary outcome				
Need for intubation	1.81 (0.89–3.67)	.103	1.70 (0.66–4.37)	.271
Secondary outcomes				
Acute kidney injury	0.47 (0.21–1.06)	.069	0.35 (0.13–1.01)	.060
Need for renal replacement therapy	1.99 (0.75–5.24)	.165	2.53 (0.80–7.95)	.113
Need for ECMO	1.55 (0.33–7.18)	.578	5.23 (0.42–65.05)	.198
Hospital length of stay (days)	1.56 (1.45–1.68)[b]	<.001[c]	1.29 (1.18–1.41)[b]	<.001[c]
Death during hospitalization	1.43 (0.59–3.44)	.427	1.91 (0.58–6.29)	.290

Abbreviations: HFNC, high flow nasal cannula; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.
[a]Statistical comparison of the data were performed using logistic regression analysis unless otherwise noted.
[b]Incident rate ratio by Poisson regression analysis.
[c]Statistical comparison performed using Poisson regression analysis.

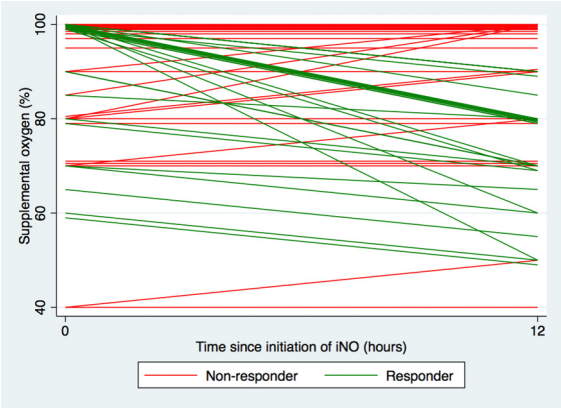

Figure 2. Individual patient response to inhaled nitric oxide at baseline and after 12 h of continuous therapy.

significant cardiac or pulmonary disease. Given the limits of our study design, patient factors predictive of iNO response and clinical outcomes of responders deserve additional attention in future studies.

Previous results of the use of iNO in patients receiving mechanical ventilation for the management of ARDS have demonstrated a transient improvement in oxygenation, but increased rates of acute kidney injury.[9,10] In our cohort, there was a trend towards a decreased risk of acute kidney injury in those that received iNO, however, the risk of subsequent need for renal replacement therapy was numerically higher in those patients that received iNO. This discrepancy and the effects of iNO on renal outcomes in spontaneously breathing patients also deserve specific attention in future trials.

Transient improvement in oxygenation with the use of iNO has been demonstrated in small studies in patients with COVID-19, although the magnitude of improvement and the effect on clinical outcomes remains unclear. Our study provides further support that iNO may improve oxygenation when administered to some spontaneously breathing patients with COVID-19. However, this effect was inconsistently observed and not related to improved clinical outcomes. Limited prior data in patients with severe COVID-19 has suggested that pulmonary vasodilation may play a role in the disease pathogenesis.[26,27] This prior observation may limit the expected improvement in ventilation-perfusion matching anticipated to be elicited by an inhaled pulmonary vasodilator and therefore, partially explain the limited response to iNO noted in our study. We postulate that the observed increase in hospital length of stay related to the use of iNO could be due to transient improvement in respiratory parameters that may delay inevitable clinical deterioration. Further, transient improvement in respiratory parameters may falsely reassure clinicians and thus, partially account for the decreased rate of self-proning (another rescue therapy) in the group of patients that received iNO. Similarly, use of rescue iNO may reflect an overall effort by clinicians to delay implementation of mechanical ventilation which could also serve to increase overall length of stay.

This analysis has a few limitations. First, this was a retrospective observation study reflecting a reexamination of an existing database of patients treated with COVID-19. Though the use of noninvasive ventilation was rare during the study period at our institution, patients that received this therapy were excluded from data collection. This exclusion limits generalizability of our findings. Further, because iNO therapy was not assigned in a random fashion, selection and survivorship biases with salvage use of iNO in the sickest patients may have confounded the results. Though attempts were made to correct for the effects of covariates and to utilize subgroup analysis to account for immortal time bias, all sources of bias, including prescriber preference for various rescue therapies, may not have been accounted for and likely cannot be in the absence of a randomized clinical trial. While most of the baseline clinical characteristics were otherwise similar between the groups, patients treated with iNO were less likely to have engaged in self-proning while simultaneously more likely to have received other adjunctive therapies in the management of COVID-19 associated respiratory failure. We suspect these differences in applied therapies may have reflected clinician efforts to avoid the need for mechanical ventilation and acknowledge this treatment difference may have confounded outcome differences between the groups. Conceivably, the physiologic effect of selective pulmonary vasodilation generated by iNO may result in improved ventilation-perfusion matching in patients undergoing self-proning. Notably, in our experience, the technical administration of iNO in patients undergoing self-proning is unchanged from the protocol used to administer the therapy to supine patients. Potential physiologic response related to the administration of iNO likely may have been best reflected by a change in the arterial oxygen saturation. However, given the retrospective design of this study, this physiologic data was not available for comparison in the majority of patients. Additionally, given the small sample size of the study population, it is feasible our study lacked the statistical power to detect differences in clinical outcomes between groups. Given these limitations, further prospective study is required to confirm our findings.

In conclusion, in this cohort of patients with respiratory failure related to COVID-19, iNO delivered via HFNC did not result in reduced oxygen requirement in the majority of patients nor was it associated with a reduction in the need for mechanical ventilation or improvement in other clinical outcomes. Despite the physiologic appeal of iNO as a sensible rescue therapy in hypoxemic respiratory failure related to COVID-19, our results add to the growing weight of evidence that iNO may be of limited utility when employed in this manner. Given the cost of continuous iNO and the observed association with increased length of stay, judicious selection of patients most likely to benefit from this therapy is warranted.

Table 6. Characteristics of Patients Stratified by Response to Inhaled Nitric Oxide at 12 h After Initiation of iNO.

	All patients	Nonresponders	Responders	*P* value
	N = 55	*N* = 29	*N* = 26	
Age (years)	55 ± 12	56 ± 13	60 ± 12	.272
Gender, women	19 (34.5)	9 (31.0)	10 (38.5)	.584
Race, nonwhite	52 (94.5)	26 (89.7)	26 (100.0)	.238
Body mass index (kg/m^2)	27.5 (24.2, 32.9)	29.0 (24.3, 33.5)	26.6 (23.8, 30.0)	.328
Comorbid diseases				
No known comorbid disease	30 (54.5)	16 (55.2)	14 (53.8)	.999
Obstructive lung disease	1 (1.8)	1 (3.4)	0 (0)	.999
Clinical data at time of initiation of HFNC				
Heart rate (bpm)	92 (80, 105)	90.5 (80, 104)	96 (83, 110)	.363
Mean arterial pressure (mm g)	92.2 ± 11.9	93.0 ± 9.9	91.3 ± 14.3	.630
Respiratory rate (per min)	30 (26, 38)	30 (25, 37)	30 (27, 39)	.421
Oxygen saturation	92 (88, 95.5)	93 (90, 96)	90.5 (87, 94)	.099
SOFA score	2.5 (1.0, 4.0)	2.0 (1.0, 4.0)	4.0 (1.0, 4.0)	.278
WBC ($\times 10^9$ per mL)	8.3 (6.1, 11.5)	8.3 (6.1, 11.0)	8.8 (6.2, 12.0)	.533
NLR ratio	6.5 (5.0, 11.2)	6.4 (5.2, 9.4)	7.5 (4.3, 12.0)	.633
Lactate (mmol/L)	1.9 (1.4, 2.4)	1.6 (1.5, 2.3)	2.1 (1.4, 3.0)	.223
CRP (mg/L)	20.5 (12.4, 25.7)	20.5 (12.7, 26.6)	20.2 (11.5, 24.3)	.876
D-dimer (μg/mL)	1.2 (0.8, 2.7)	1.0 (0.8, 1.7)	1.8 (1.2, 3.8)	.019
Procalcitonin (ng/mL)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	0.2 (0.1, 0.4)	.880
Management strategy				
Initial iNO dose >20 ppm	12 (21.8)	3 (10.3)	9 (34.6)	.048
Supplement O_2 (%) baseline	100 (80, 100)	95 (80, 100)	100 (80, 100)	.422
HFNC flow (L/min) at baseline	50 (50, 60)	50 (50, 60)	50 (50, 60)	.707
Supplement O_2 (%) 12 h	80 (70, 100)	100 (80, 100)	75 (65, 80)	<.001
HFNC flow (L/min) 12 h	50 (50, 60)	50 (50, 60)	50 (50, 60)	.506

Data presented as mean ± standard deviation, median (25th percentile, 75th percentile), or *n* (%) unless otherwise indicated.
Abbreviations: INO, inhaled nitric oxide; HFNC, high flow nasal cannula; SOFA, sequential organ failure assessment; WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio; CRP, c-reactive protein.

Any future prospective evaluation of iNO for use in COVID-19 should focus on discerning if a certain patient phenotype with COVID-19 is most likely to benefit from this therapy. Strict adherence to isolation of use of iNO to "responders" may increase the likelihood of identifying a clinical response in the context of a clinical trial.

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Author Contributions

AC and CSK are the guarantors of the content of the manuscript and contributed to all aspects of the project. SP, KA, SA, AWB, DS, VK, OAS, AS, AWH, MD, and SDN contributed substantially to project design, data collection, and

data analysis. PC provided assistance with project design and implementation. All authors helped prepare and review the final manuscript.

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REFERENCES

1. Gattinoni L, Coppola S, Cressoni M, et al. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2020;201(10):1299-1300. doi:10.1164/rccm.202003-0817LE.
2. Chang R, Elhusseiny KM, Yeh Y-C, et al. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes—A systematic review and meta-analysis. *PLoS ONE.* 2021;16(2):e0246318. doi:10.1371/journal.pone.0246318.
3. Demoule A, Baron AV, Darmon M, et al. High-flow nasal cannula in critically III patients with severe COVID-19. *Am J Respir Crit Care Med.* 2020;202(7):1039-1042. doi:10.1164/rccm.202005-2007LE.
4. Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. *Respir Care.* 2016;61(4):529. doi:10.4187/respcare.04577.
5. Chandel A, Patolia S, Brown AW, et al. High-flow nasal cannula in COVID-19: outcomes of application and examination of the ROX index to predict success. *Respir Care.* 2020. doi:10.4187/respcare.08631.
6. Saunders JL, Davis MD. 2020 Year in review: pharmacologic treatments for COVID-19. *Respir Care.* 2021;66(7):1167. doi:10.4187/respcare.09153.
7. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled nitric oxide in ARDS study group. *Crit Care Med.* 1998;26(1):15-23. doi:10.1097/00003246-199801000-00011.
8. Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med.* 2005;353(25):2683-2695. doi:10.1056/NEJMra051884.
9. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Crit Care Med.* 2014;42(2):404-412. doi:10.1097/CCM.0b013e3182a27909.
10. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev.* 2016(6):CD002787. doi:10.1002/14651858.CD002787.pub3.
11. Davis SL, Crow JR, Fan JR, et al. Use and costs of inhaled nitric oxide and inhaled epoprostenol in adult critically ill patients: a quality improvement project. *Am J Health Syst Pharm.* 2019;76(18):1413-1419. doi:10.1093/ajhp/zxz151.
12. Tzanetos DR T, Housley JJ, Barr FE, et al. Implementation of an inhaled nitric oxide protocol decreases direct cost associated with its use. *Respir Care.* 2015;60(5):644. doi:10.4187/respcare.03308.
13. Akerstrom S, Mousavi-Jazi M, Klingstrom J, et al. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *J Virol.* 2005;79(3):1966-1969. doi:10.1128/JVI.79.3.1966-1969.2005.
14. Fang W, Jiang J, Su L, et al. The role of NO in COVID-19 and potential therapeutic strategies. *Free Radic Biol Med.* 2021;163:153-162. doi:10.1016/j.freeradbiomed.2020.12.008.
15. Bagate F, Tuffet S, Masi P, et al. Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. *Ann Intensive Care.* 2020;10(2020):151. doi:10.1186/s13613-020-00769-2.
16. Longobardo A, Montanari C, Shulman R, et al. Inhaled nitric oxide minimally improves oxygenation in COVID-19 related acute respiratory distress syndrome. *Br J Anaesth.* 2021;126(1):e44-e46. doi:10.1016/j.bja.2020.10.011.
17. Ferrari M, Santini A, Protti A, et al. Inhaled nitric oxide in mechanically ventilated patients with COVID-19. *J Crit Care.* 2020;60:159-160. doi:10.1016/j.jcrc.2020.08.007.
18. Parikh R, Wilson C, Weinberg J, et al. Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients. *Ther Adv Respir Dis.* 2020;14(1):1753466620933510. doi:10.1177/1753466620933510.
19. Tavazzi G, Pozzi M, Mongodi S, et al. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia. *Crit Care* 2020;24(2020):508. doi:10.1186/s13054-020-03222-9.
20. Abou-Arab O, Huette P, Debouvries F, et al. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. *Crit Care* 2020;24(2020):645. doi:10.1186/s13054-020-03371-x.
21. Wiegand SB, Safaee Fakhr B, Carroll RW, et al. Rescue treatment with high-dose gaseous nitric oxide in spontaneously breathing patients with severe coronavirus disease 2019. *Crit Care Explor.* 2020;2(11):e0277. doi:10.1097/cce.0000000000000277.
22. Bellerophon Therapeutics. Bellerophon Therapeutics Announces Results of Interim Analysis of Phase 3 COViNOX Study of INOpulse® for the Treatment of COVID-19. 2020.
23. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003;289(22):2983-2991. doi:10.1001/jama.289.22.2983.
24. Berger JS, Kunichoff D, Adhikari S, et al. Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19. *Arterioscler Thromb Vasc Biol.* 2020;40(10):2539-2547. doi:10.1161/ATVBAHA.120.314872.
25. Kline JA, Puskarich MA, Jones AE, et al. Inhaled nitric oxide to treat intermediate risk pulmonary embolism: a multicenter randomized controlled trial. *Nitric Oxide* 2019;84:60-68. doi:10.1016/j.niox.2019.01.006.
26. Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis.* 2020;20(12):1365-1366. doi:10.1016/s1473-3099(20)30367-4.
27. Reynolds AS, Lee AG, Renz J, et al. Pulmonary vascular dilatation detected by automated transcranial Doppler in COVID-19 pneumonia. *Am J Respir Crit Care Med.* 2020;202(7):1037-1039. doi:10.1164/rccm.202006-2219LE.