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The Use of High-Flow Nasal Oxygen in the ICU as a First-Line Therapy for Acute Hypoxemic Respiratory Failure Secondary to Coronavirus Disease 2019

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Objectives: Limited evidence is available regarding the role of high-flow nasal oxygen in the management of acute hypoxemic respiratory failure secondary to coronavirus disease 2019. Our objective was to characterize outcomes associated with high-flow nasal oxygen use in critically ill adult patients with coronavirus disease 2019-associated acute hypoxemic respiratory failure.

Design: Observational cohort study between March 18, 2020, and June 3, 2020.

Setting: Nine ICUs at three university-affiliated hospitals in Philadelphia, PA.

Patients: Adult ICU patients with confirmed coronavirus disease 2019 infection admitted with acute hypoxemic respiratory failure.

Interventions: None.

Measurements and Main Results: Of 266 coronavirus disease 2019 ICU admissions during the study period, 124 (46.6%) received some form of noninvasive respiratory support. After exclusions, we analyzed 83 patients who were treated with high-flow nasal oxygen as a first-line therapy at or near the time of ICU admission. Patients were predominantly male (63.9%). The most common comorbidity was hypertension (60.2%). Progression to invasive mechanical ventilation was common, occurring in 58 patients (69.9%). Of these, 30 (51.7%) were intubated on the same day as ICU admission. As of June 30, 2020, hospital mortality rate was 32.9% and the median hospital length of stay was 15 days. Among survivors, the most frequent discharge disposition was home (51.0%). In comparing patients who received high-flow nasal oxygen alone ($n = 54$) with those who received high-flow nasal oxygen in conjunction with noninvasive positive-pressure ventilation via face mask ($n = 29$), there were no differences in the rates of endotracheal intubation or other clinical and utilization outcomes.

Conclusions: We observed an overall high usage of high-flow nasal oxygen in our cohort of critically ill patients with acute hypoxemic respiratory failure secondary to coronavirus disease 2019. Rates of endotracheal intubation and mortality in this cohort were on par with and certainly not higher than other published series. These findings should prompt further considerations regarding the use of high-flow nasal oxygen in the management algorithm for coronavirus disease 2019-associated acute hypoxemic respiratory failure.

Key Words: coronavirus; critical care; high-flow nasal oxygen; intubation, intratracheal; noninvasive ventilation; respiratory distress syndrome, adult

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The role of noninvasive respiratory support strategies in the management of acute hypoxemic respiratory failure (AHRF) secondary to coronavirus disease 2019 (COVID-19) is not well defined. Early in the pandemic, anecdotal guidance favored early endotracheal intubation, given rapidly escalating oxygen requirements seen in infected individuals and concerns for viral aerosolization with the use of high-flow nasal oxygen (HFNO) or noninvasive positive-pressure ventilation (NIV). As international experience with COVID-19 has grown, there have been calls for a more nuanced approach to decisions regarding endotracheal intubation, with more consideration given to

noninvasive respiratory support strategies early in the disease course (1, 2).

The optimal mode of noninvasive respiratory support in COVID-19-associated AHRF is unknown. The Society of Critical Care Medicine recommends HFNO over NIV for COVID-19-associated AHRF (3). However, due to lack of data specific to COVID-19, this recommendation comes as an extrapolation of evidence from other critically ill patient populations. HFNO in particular has been shown to be effective in preventing reintubation in other non-COVID disease states (4, 5) and may even confer a mortality benefit compared with standard oxygen therapy or NIV when applied to patients with nonhypercapnic acute respiratory failure (6). Among COVID-19 patients, successful treatment with HFNO and avoidance of intubation has been reported among patients with less severe hypoxemia in a small study from China (7). Utilization of HFNO, however, appears variable in clinical practice, with only 5% trialed on this modality in a New York City COVID-19 cohort and 21% in an early cohort of hospitalized patients from Wuhan, China (8, 9). Overall, experiences with use of HFNO in COVID-19-associated AHRF have not been extensively described in the literature.

In light of evolving opinion and limited evidence, we sought to describe the characteristics and outcomes of adult patients with AHRF secondary to COVID-19 who were treated with HFNO as a first-line therapy at or near the time of ICU admission.

MATERIAL AND METHODS

This is an observational cohort study of critically ill patients with COVID-19-associated AHRF who received HFNO as a first-line therapy at or near the time of ICU admission. This cohort was screened from a larger cohort of critically ill patients with COVID-19 who were admitted to nine ICUs (99 beds) at three Thomas Jefferson University hospitals in Philadelphia, PA, between March 18, 2020, and June 3, 2020. All patients had laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection via polymerase chain reaction assay of primarily nasopharyngeal swabs, with the adjunct of lower respiratory tract aspirates, as clinically indicated. During the time of this study, all patients were managed under a high-intensity ICU model of staffing, irrespective of the unit to which they were admitted (10). There were no critical shortages in beds, staffing, ventilators, or other supplies.

Patients were included if they received HFNO alone, or HFNO in sequential conjunction with NIV delivered by face mask, as a first-line therapy at or near the time of ICU admission. The decision to initiate HFNO as well as the individual settings of the HFNO device (Fisher & Paykel, Auckland, New Zealand, or Vapotherm, Exeter, NH) were at the discretion of the attending physician. We excluded patients with limitations to their care at ICU admission (e.g., do not resuscitate [DNR] and/or do not intubate [DNI]), as this may have affected the decision to use noninvasive respiratory support strategies. We also excluded patients who received NIV alone in our analyses to avoid patients with hypercapnia as the primary driver of their respiratory failure. The primary outcome of interest was progression to invasive mechanical ventilation. Secondary outcomes included ICU and hospital mortalities and length of stay (LOS).

Clinical, demographic, and therapeutic data were chart-abstracted from the electronic medical record and stored in a password-protected online data repository, research electronic data capture, accessible to key study personnel (11). To compare patients who received HFNO alone with those who received HFNO in sequential conjunction with NIV, we used chi-square or Fisher exact for categorical variables, and Wilcoxon rank-sum for continuous variables, as appropriate. A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed with Stata 15.1 (Statacorp, College Station, TX). The study was approved by Jefferson's Office of Human Research Institutional Review Board (20E.414) with a waiver of informed consent.

RESULTS

Admission Characteristics

From March 18, 2020, to June 3, 2020, there were 266 admissions to the ICU for patients infected with SARS-CoV-2, of which 15 (5.6%) were nonindex ICU admissions (i.e., readmissions to the ICU during the same hospital stay). Overall, 124 (46.6%) of all COVID-19 ICU admissions received some form of noninvasive respiratory support at the time of or immediately prior to ICU admission. After exclusions, we identified 83 patients who were treated with HFNO as a first-line therapy, of which 54 received HFNO alone and 29 received HFNO in sequential conjunction with NIV (**Fig. 1**).

Patient characteristics of the HFNO cohort are summarized in **Table 1**. Among these 83 patients, the median age was 65 years (interquartile range [IQR], 55–76), with 54.2% of patients 65 years old or older. Patients were predominantly male (63.9%) and Black (44.6%). The most common comorbidity was hypertension (60.2%), followed by diabetes mellitus (53%). Other chronic illnesses such as malignancy, cerebrovascular accident, and end-stage renal disease were uncommon. Most patients in the study originated from the floor rather than directly from the emergency department prior to ICU admission.

The median Acute Physiology and Chronic Health Evaluation (APACHE) II score in this cohort was 23 (IQR, 16–30). Nearly all patients had inflammatory markers drawn, the median peak values of which were elevated far above reference ranges (**Table 2**).

Interventions and Outcomes

Systemic anticoagulation was newly started in 24 patients (28.9%), with venous thromboembolic events (i.e., pulmonary embolism or deep vein thrombosis) confirmed in six patients (7.2%). Systemic steroids were newly administered in 38 patients (45.8%), with the predominant indication for steroids being COVID-19 pneumonia (22, 57.9%) (Table 2).

Progression to invasive mechanical ventilation was common and occurred in 58 patients (69.9%) (**Table 3**). Of these, 30 (51.7%) were intubated on the same day as ICU admission. The median postintubation Pao_2:Fio_2 ratio was 130 mm Hg (IQR, 97–210) (Table 2). The median duration on the ventilator was 9 days

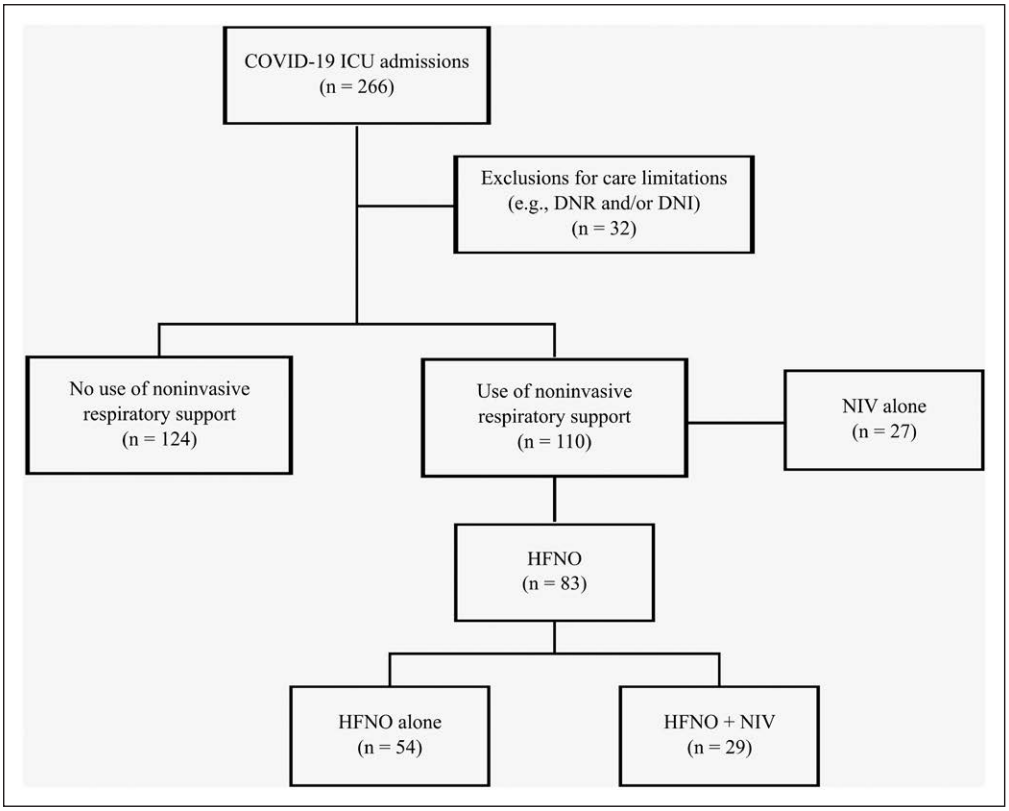

Figure 1. Patient-selection process. COVID-19 = coronavirus disease 2019, DNI = do not intubate, HFNO = high-flow nasal oxygen, NIV = noninvasive positive-pressure ventilation.

(IQR, 4.5–24.5 d), and tracheostomy was ultimately performed in 17 patients (29.3%) (Table 3).

As of June 30, 2020, one patient remained admitted to the ICU on invasive mechanical ventilation, and six additional patients were still hospitalized after leaving the ICU. Among patients with available discharge data, ICU mortality was 29.3% (24/82) and overall hospital mortality was 32.9% (25/76). The mortality outcomes of these patients who received HFNO as first-line therapy did not differ significantly from those who received no noninvasive respiratory support at or near the time of ICU admission (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCX/A387). At the time of death in the ICU, 21 patients (87.5%) had some form of care limitations (e.g., DNR/DNI or withdrawal of life support). Median ICU and hospital LOS were 9 days (IQR, 4–17 d) and 15 days (IQR, 10–26.5 d), respectively. Among survivors to hospital discharge, the most frequent discharge disposition was home (51.0%), followed by acute rehabilitation facility (27.5%) (Table 3).

Comparison of HFNO-Alone Group With HFNO + NIV Group

We conducted additional analyses to compare the 54 patients who received HFNO alone with the 29 patients who received HFNO in sequential conjunction with NIV. Demographics were similar between the two groups, as were comorbidities, with the exception of heart failure, which was more common in the group to which NIV was also applied. There was no difference in the median APACHE II scores between the two groups. Postintubation Pao_2:FIO_2 ratios were significantly lower among patients who received HFNO in conjunction with NIV, and these patients were also more likely to receive inhaled vasodilator therapy. New systemic anticoagulation and systemic steroids were administered equally between the two groups (**Table 4**).

Neither category of noninvasive respiratory support was more successful at preventing or delaying endotracheal intubation. Furthermore, there was no significant difference in the duration of invasive mechanical ventilation, tracheostomy rates, ICU and hospital mortality, and ICU and hospital LOS between the two groups (Table 4).

DISCUSSION

During the initial COVID-19 experience at our institution, we demonstrated an overall high usage of noninvasive respiratory support modalities for critically ill patients with AHRF secondary to COVID-19. Nearly half of all COVID-19 ICU admissions received some degree of noninvasive respiratory support in the form of HFNO and/or NIV as a first-line therapy, and 96 patients (36.1%) were treated, at least in part, with HFNO at or near the time of ICU admission.

After exclusions of patients with care limitations, we analyzed 83 ICU admissions (31.2%), in which HFNO was employed as a first-line therapy, alone or in sequential conjunction with NIV via face mask. We showed that progression to invasive mechanical ventilation was common and occurred early. However, despite a high index of illness severity recorded at ICU admission, approximately two-thirds of patients survived to hospital discharge, and among these survivors, over half returned to home. We additionally showed that there were no differences in outcomes among patients who received HFNO alone, compared with those who received HFNO in sequential conjunction with NIV.

The high utilization rate of HFNO seen in our study differs considerably from the 5% reported in a New York City ICU cohort during their regional peak of the pandemic (8). Similarly, in an ICU cohort from Tongji, China, only 10.2% of patients were treated with HFNO (12). In Lombardy, Italy, 137 critically ill patients (11%) used some form of noninvasive support, although it is uncertain where HFNO fell into their care algorithm (13). It is possible that the higher HFNO utilization in our cohort is explained by the timing of the onset and peak of the pandemic in Pennsylvania, which lagged that of China, Italy, and even New York by at least a month or more. As such, there may have been

TABLE 1. Patient Demographic and Admission Characteristics

Characteristic (*n* [%] Unless Otherwise Indicated)	Total (*n* = 83)
Age, median (IQR)	65 (55–76)
Age ≥ 65	45 (54.2)
Male	53 (63.9)
Race	
Black	37 (44.6)
White	21 (25.3)
Hispanic	11 (13.3)
Asian/Pacific-islander	13 (15.7)
Other/unknown	1 (1.2)
Body mass index, median (IQR)	29.3 (24.9–33.5)
≥ 30 kg/m^2	36 (43.4)
Smoking status	
Active	5 (6.0)
Former	35 (42.2)
Never	36 (43.4)
Unknown	7 (8.4%)
Comorbidities	
Hypertension	50 (60.2)
Diabetes mellitus	44 (53.0)
Congestive heart failure	18 (21.7)
Chronic obstructive pulmonary disease/ asthma	16 (19.3)
Coronary artery disease	15 (18.1)
Cancer	9 (10.8)
Cerebrovascular accident	7 (8.4)
End-stage renal disease	5 (6.0)
Nonindex ICU admission	4 (4.8)
Admission source	
Home	64 (77.1)
Nursing home	14 (16.9)
Other/unknown	5 (6.0)
Care site immediately prior to ICU	
Floor	47 (56.6)
Emergency department	27 (32.5)
Step-down unit	9 (10.8)
Symptom duration prior to presentation (d)	
< 7	40 (48.2)
7–14	31 (37.3)
> 14	5 (6.0)
Unknown	7 (8.4)

IQR = interquartile range.

TABLE 2. Clinical Characteristics and ICU Interventions

Characteristic (*n* [%] Unless Otherwise Indicated)	Total (*n* = 83)	Reference Range
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	23 (16–30)	
Laboratory values,[a] median (IQR)		
Peak D-dimer (ng/mL)	4,502 (1,946–14,613)	< 230
Peak C-reactive protein (mg/dL)	26.9 (15.6–34.7)	≤ 0.80
Peak ferritin (ng/mL)	1,375 (763–2,507)	30–400
Pao_2:Fio_2,[b] median (IQR)	130 (97.0–210.5)	
Interventions		
Inhaled pulmonary vasodilator	9 (10.8)	
New systemic anticoagulation	24 (28.9)	
New systemic steroids	38 (45.8)	
New initiation of renal replacement therapy	9 (10.8)	
Prone ventilation	28 (48.3)	
Extracorporeal membrane oxygenation	2 (2.4)	

IQR = interquartile range.
[a]Three missing values.
[b]Postintubation values only, two missing values.
[c]Refers to % proned in 58 mechanically ventilated patients only.

increased comfort with trialing noninvasive respiratory strategies due to this delay and, in the setting of absent evidence, a willingness to gauge its impact on patient outcomes.

It remains unknown whether HFNO in COVID-19-associated AHRF can prevent progression to invasive mechanical ventilation or affect overall mortality. At our institution, the endotracheal intubation rate for the entire ICU cohort prior to exclusions was approximately 70%, which is on the lower end of the 75–88% range reported in other published COVID ICU cohorts, both domestically and abroad (8, 13–15). In our analyzed cohort of 83 patients with no care limitations, who received HFNO as a first-line therapy on ICU admission, the overall endotracheal intubation rate was 69.9%. Additionally, the ICU mortality rate of 29.3% in our cohort of HFNO patients is significantly lower than previously reported mortality rates, which have ranged from 42.5% to 78% among other COVID-19 ICU patient cohorts (13, 16, 17). The reason for our lower observed rates of endotracheal intubation without a higher ICU mortality compared with other published reports is unclear and may be multifactorial. At the very least, our findings are encouraging in that patients with COVID-19-associated AHRF who received HFNO as a first-line therapy did not have worse outcomes. Optimistically, our findings may perhaps even suggest that patients with COVID-19-associated AHRF who receive HFNO as a first-line therapy may have better

TABLE 3. Clinical Outcomes

Outcome (*n* [%] Unless Otherwise Indicated)	Total (*n* = 83)
Invasive mechanical ventilation	58 (69.9)
Time to intubation (d), median (IQR)	0 (0–1)
Ventilator days,[a] median (IQR)	9 (4.5–24.5)
Tracheostomy[b]	17 (29.3)
ICU mortality	24 (29.3)
Hospital mortality	25 (32.9)
ICU LOS (d),[a] median (IQR)	9 (4–17)
Hospital LOS (d),[c] median (IQR)	15 (10–26.5)
Hospital discharge disposition[c,d]	
Home	26 (51.0)
Long-term acute care	5 (9.8)
Skilled nursing facility	5 (9.8)
Rehabilitation facility	14 (27.5)
Nursing home	1 (2.0)

IQR = interquartile range, LOS = length of stay.

[a]Excludes one patient still on mechanical ventilation in the ICU as of June 30, 2020.

[b]Refers to % tracheostomized in 58 mechanically ventilated patients only.

[c]Excludes seven patients still hospitalized as of June 30, 2020.

[d]Refers to disposition among survivors to hospital discharge only.

outcomes than initially expected based on anecdotal guidance early in the pandemic. This should prompt clinicians and researchers to explore further as to when, for whom, and how HFNO can be used in the algorithm for AHRF in COVID-19.

The relative benefits of various noninvasive respiratory support strategies for the management of (non-COVID-19) AHRF have previously been explored. Although the landmark high FLow nasal Oxygen in the Resuscitation of patients with Acute Lung Injury trial in 2015 popularized the use of HFNO in the treatment of AHRF by showing a reduction in 90-day mortality, the primary outcome of progression to endotracheal intubation was not significantly different between the use of HFNO, NIV, and standard oxygen therapy in this study (6). Likewise, other randomized controlled trials exploring whether HFNO can prevent endotracheal intubation compared with other noninvasive modalities have additionally produced conflicting results (18–22). These varying findings are likely due to the heterogeneity that exists in the underlying etiologies and clinical courses of AHRF, coupled with the heterogeneity in the studies comparing various combinations of noninvasive respiratory support modalities (e.g., HFNO vs NIV via face mask, or HFNO vs standard oxygen therapy) (23). These nuances may be especially important to consider with a novel respiratory disease such as COVID-19, which may have its own unique phenotype(s) (24, 25). Thus, beyond the findings from our study, further investigation is warranted to guide clinicians in understanding the role of HFNO and/or NIV in potentially delaying or avoiding endotracheal intubation without sacrificing favorable patient outcomes.

One major concern among clinicians with using HFNO in AHRF secondary to COVID-19 is the possible risk of increased aerosolization of viral particles. However, it remains unknown how significant this risk may be. At our institution, it is unknown whether any cases of healthcare worker infection could be directly linked to HFNO exposure. It has been suggested that the aerosolization of respiratory particles with HFNO is similar to that of other oxygen support modalities such as a standard oxygen mask (26). Similarly, a recent systematic review could not identify demonstrative evidence in either support or rejection of this concern (27). A salient risk factor for nosocomial infections of healthcare workers described during the current COVID-19 pandemic has included a lack of proper personal protective gear, and infections were more likely to occur earlier in the pandemic when preparations of personnel and resources were likely to have been archaic (28). In this context, HFNO should continue to be viewed as a viable strategy for use in AHRF secondary to COVID-19, but one that needs further exploration of the risk-benefit scale in terms of patient outcomes, local resources, and healthcare worker safety.

Our study has several limitations, including its retrospective nature. First, the utilization of HFNO with NIV was not protocolized. Although many patients were often stepped-up to NIV from HFNO at or near the time of ICU admission, the order and duration of use of either modality were at the discretion of the treating physician. The sequential and alternating use of HFNO and NIV has been examined in its ability to affect patient comfort, ventilatory parameters, and oxygenation in non-COVID AHRF, but not rates of intubation (29). Our descriptive study also precludes conclusions about whether their dual use can avoid intubation in some patients. Second, our study took place at three hospitals in Philadelphia, PA, potentially limiting generalizability to other institutions serving patients with differing demographics and socioeconomic vulnerabilities. Additionally, locoregional differences in the availability of personnel and hospital resources could affect viability of using HFNO during a pandemic surge. Finally, because our focus was on COVID-19 patients with ICU needs, it is possible that more patients successfully treated with HFNO were kept on the wards and, therefore, were not included in our analyses.

CONCLUSIONS

In our critically ill cohort of patients with AHRF secondary to COVID-19, we saw high rates of HFNO utilization, with intubation and mortality rates that were on par with and certainly not higher than other published series. Some have argued that the risk of spontaneous respiratory efforts in AHRF may, at times, preclude consideration of noninvasive strategies (30). However, the avoidance of invasive mechanical ventilation along with its inherent complications is not an unreasonable approach in select patients. Our study findings should prompt clinicians and researchers to explore further the role of HFNO as a viable strategy in the algorithm for COVID-19-associated AHRF. As the decision to intubate patients with AHRF is clinical, often based on physician judgment, further trials examining the use of HFNO specifically in COVID-19 will hopefully provide guidance about the "who, when, and how" of using noninvasive respiratory support strategies during this pandemic.

TABLE 4. Demographics, Admission and Clinical Characteristics, ICU Interventions, and Outcomes for Subgroups

Characteristic (*n* [%] Unless Otherwise Indicated)	HFNO Alone (*n* = 54)	HFNO + Noninvasive Positive-Pressure Ventilation (*n* = 29)	*p*
Key demographics			
Age, median (IQR)	65 (56-78)	67 (53-75)	0.92
Male	33 (61.1)	20 (69.0)	0.48
Race			0.43
Black	21 (38.9)	16 (55.2)	
White	15 (27.8)	6 (20.7)	
Other	18 (33.3)	7 (24.1)	
Body mass index, median (IQR)	28.4 (24.6-32.5)	30.4 (26.3-34)	0.15
Comorbidities			
Hypertension	32 (59.3)	18 (62.1)	0.80
Diabetes mellitus	30 (55.6)	14 (48.3)	0.53
Congestive heart failure	8 (14.8)	10 (34.5)	0.04
Chronic obstructive pulmonary disease/asthma	8 (14.8)	8 (27.6)	0.16
Key clinical characteristics and ICU interventions			
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	23 (16–29)	23 (18–33)	0.27
Pao_2:FIO_2,[a] median (IQR)	157 (106-224)	107 (84-183.5)	0.04
Interventions			
Inhaled pulmonary vasodilator	2 (3.7)	7 (24.1)	0.01
New systemic anticoagulation	16 (29.6)	8 (27.6)	0.85
New systemic steroids	21 (38.9)	17 (58.6)	0.09
New initiation of renal replacement therapy	4 (7.4)	5 (17.2)	0.27
Prone ventilation[b]	17 (47.2)	11 (50.0)	0.84
Extracorporeal membrane oxygenation	1 (1.9)	1 (3.4)	1.00
Key clinical outcomes			
Invasive mechanical ventilation	36 (66.7)	22 (75.9)	0.38
Time to intubation (d), median (IQR)	0.5 (0-1)	0 (0-1)	0.91
Ventilator days,[c] median (IQR)	8 (4.5-20)	11 (4–30)	0.52
Tracheostomy[d]	10 (27.8)	7 (31.8)	0.74
ICU mortality	15 (27.8)	9 (32.1)	0.68
Hospital mortality[e]	16 (30.8)	9 (37.5)	0.56
ICU LOS,[c] median (IQR)	8 (4–13)	11.4 (4-19.5)	0.37
Hospital LOS,[e] median (IQR)	14.5 (9.5-25.5)	19.5 (12-28.5)	0.21

HFNO = high-flow nasal oxygen, IQR = interquartile range, LOS = length of stay.
[a]Postintubation values only.
[b]Refers to % proned in 58 mechanically ventilated patients only.
[c]Excludes one patient still on mechanical ventilation in the ICU as of June 30, 2020.
[d]Refers to % tracheostomized in 58 mechanically ventilated patients only.
[e]Excludes seven patients still hospitalized as of June 30, 2020.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

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