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Ratio of oxygen saturation index for predicting high-flow nasal cannula outcomes in emergency department for COVID-19 patients with severe hypoxemia: A retrospective study

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Abstract:

OBJECTIVES: High-flow nasal cannula (HFNC) oxygen therapy has been used as an initial ventilatory support for coronavirus disease 2019 (COVID-19) patients with mixed levels of acute hypoxemic respiratory failure (AHRF). However, the effectiveness of HFNC when used as initial ventilatory support in COVID-19 patients with severe AHRF exclusively is not well documented. Ratio of oxygen saturation (ROX) index (ROX = [SpO_2/fraction of inspired oxygen]/respiratory rate) was shown to predict the outcome of HFNC in intensive care unit patients. Our study aimed to evaluate the utility of the ROX index for predicting HFNC therapy success/failure in COVID-19 patients with severe AHRF when HFNC is used as the first line of ventilatory support.

METHODS: Retrospective study in 67 COVID-19 patients with severe AHRF receiving HFNC in the emergency department at a tertiary care academic medical center. ROX index was determined at 0, 2, 6, 12, and 24 h of HFNC onset. The need to escalate to noninvasive or invasive ventilatory support was documented. The receiver operating characteristic curves were performed and areas under the curves (AUCs) were calculated to evaluate the accuracy of ROX index for differentiating between patients who will succeed or fail HFNC therapy.

RESULTS: HFNC therapy was successful in 19 patients (28.1%) and failed in 48 patients (71.6%). ROX index after 6 h of HFNC initiation had the best predictive capacity for the outcome of HFNC therapy (AUC = 0.78). ROX index >4.4 at 6 h of HFNC onset was significantly associated with HFNC success/failure.

CONCLUSION: ROX index at 6 h after initiating HFNC therapy in COVID-19 patients with severe AHRF has a good predictive capacity for HFNC success/failure.

Keywords:

COVID-19, emergency department, high-flow nasal cannula, hypoxemia, ratio of oxygen saturation index, severe hypoxemic respiratory failure

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Box-ED section

What is already known about the topic?

- High-flow nasal cannula (HFNC) oxygen therapy has shown promising results as first-line support in patients with acute hypoxemic respiratory failure (AHRF). However, most of the benefits have been reported in patients with mild-to-moderate AHRF. ROX, an integrative index of respiratory rate, oxygenation, and oxygen supply, has been shown to predict the failure/success of HFNC therapy.

What is the conflict on the issue? What is its importance for readers?

- The use of HFNC as first-line respiratory support in severe AHRF (PaO_2/FiO_2 <100) COVID-19 patients managed in the emergency department has not been well established since most of these patients will end up being intubated and supported with invasive mechanical ventilation
- During the COVID-19 pandemic and because of its value in serving as a bridge between nasal/nonrebreathing oxygen masks and both noninvasive and invasive mechanical ventilation as well as its capability for reducing the need for intubation and subsequently the risk of complications from mechanical ventilation, HFNC therapies were frequently attempted in patients with severe AHRF
- Confirming the utility of the ROX index for predicting HFNC therapy success/failure in COVID-19 patients with severe AHRF when HFNC is used as the first line of ventilatory support in the emergency department can be of great value.

How is the study structured?

- This was a single-center, retrospective cohort analysis of a prospectively collected observational clinical database of patients presented to the emergency department of a tertiary care academic medical center during the COVID-19 pandemic from March 2020 to March 2021.

What does this study tell us?

- In COVID-19 patients with severe hypoxemic respiratory failure who are managed in the emergency department, a ROX index of >4.4 at 6 h after HFNC initiation had a good predictive ability for HFNC therapy success.

Introduction

High-flow nasal cannula (HFNC) oxygen therapy is an easy-to-use ventilatory support modality that delivers high fractions of heated and humidified oxygen at flow rates reaching 60–100 L/min.[1] It represents a superior alternative to conventional oxygen therapy for patients with acute hypoxemic respiratory failure (AHRF).[1-3] HFNC can reduce the rate of intubation and invasive mechanical ventilation (IMV) in patients with AHRF.[4] Although HFNC may avoid the need for mechanical ventilation (MV) in some patients with AHRF, it may unduly delay the initiation of MV in others and worsen their outcome.[5] As such, it is essential to identify as early as possible patients who will fail HFNC trials so that they are escalated to more aggressive respiratory support modalities such as noninvasive ventilation (NIV) and invasive MV.

Roca *et al*. first described the ratio of oxygen saturation (ROX) index and showed that it can predict HFNC success/failure in intensive care unit (ICU) patients with AHRF.[6,7] ROX index, expressed as $(SpO_2/FiO_2)/RR$, where SpO_2 is the oxygen saturation by pulse oximetry, FiO_2 is the fraction of inspired oxygen, and RR is the respiratory rate, can be easily obtained and used at the bedside. Roca *et al*. showed that a ROX value of >4.88 determined at 12 h of HFNC therapy is a valuable predictor of patients at low risk for HFNC failure.[7]

In recent years, the coronavirus disease 2019 (COVID-19) pandemic has resulted in an unprecedented number of patients with AHRF flooding health-care facilities all over the world. ICUs were filled up quickly and COVID-19 patients were boarded in emergency departments (EDs) for substantial periods. HFNC was extensively utilized in EDs for COVID-19 patients, particularly in those with mild-to-moderate hypoxemia.[8,9] However, no data have been published about tools for predicting the outcome of HFNC when utilized as the initial form of respiratory support in COVID-19 patients with severe hypoxemia managed in ED. The aim of the current study is to assess whether the ROX index is a valuable predictor of HFNC therapy success/failure in COVID-19 patients with severe AHRF treated initially with HFNC in ED.

Methods

This study was approved by the Institutional Review Board at the (BIO-2021-0318; November 25, 2021). Given the retrospective nature of the study, no informed consent was deemed necessary.

We performed a single-center retrospective cohort analysis of a clinical database of patients treated for severe AHRF secondary to COVID-19 and immediately received HFNC (Airvo 2; Fisher and Paykel, Auckland, New Zealand) upon presentation to the ED at an academic medical center staffed with emergency medicine specialists from March 2020 to March 2021. Patients were included if ≥18 years of age, with a laboratory-confirmed diagnosis of COVID-19 by polymerase chain reaction testing, with either partial pressure of arterial oxygen $(PaO_2)/FiO_2 \leq 100$ from first

arterial blood gas results or $SpO_2/FiO_2 \leq 140$ and treated with HFNC for at least 2 h in the ED. Patients were excluded if endotracheal intubation was performed, or noninvasive bilevel positive airway pressure was applied before initiation of HFNC. Moreover, patients with a "do-not-intubate order" were excluded.

HFNC was initiated with flow of 50–60 L/min, and FiO_2 was adjusted to maintain $SpO_2 \geq 92\%$. Patients were monitored by noninvasive measurements of heart rate, blood pressure, oxygen saturation, and RR. HFNC failure was defined as escalation to noninvasive ventilatory (NIV) support or the need for intubation and initiation of MV. Escalation of therapy was generally based on the presence of hypoxemia with the inability to maintain $SpO_2 \geq 92\%$ despite receiving maximal FiO_2 and/or breathing frequency >35 breaths/min with associated signs of respiratory distress/failure.

Adjunct therapies targeting COVID-19 were administered at the discretion of the ED team and commonly included systemic glucocorticoids, remdesivir, and anticoagulation.

Data were collected from the patients' electronic medical records during December 2021–January 2022. Patients' demographics, relevant clinical data, and past medical history were obtained and followed up until patients were discharged from the ED or expired. Clinical data included heart rate, oxygen saturation, blood pressure, and RR. Laboratory data included D-dimer, procalcitonin, C-reactive protein, lactate levels, and arterial blood gases. ROX index was determined for all patients at 2 h and subsequently at 6, 12, and 24 h after initiation of HFNC therapy or until HFNC failure is observed. Acute Physiology and Chronic Health Evaluation-II scores in the first 24 h of ED stay, pneumonia severity index, and sequential organ failure assessment scores upon ED admission were determined. The incidence of intubation and MV and the use of noninvasive ventilation (NIV) were also recorded.

The main outcome was either the escalation to NIV or the need of intubation and MV both reflecting the failure of HFNC therapy. Quantitative variables were expressed as mean and standard deviation or median and interquartile range (IQR) if normality criteria, as tested with the Kolmogorov–Smirnov test, were not met. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the Student's *t*-test or Mann–Whitney *U*-test, as appropriate. For categorical variables, the comparison was made using the Chi-square test or Fisher's exact test, as appropriate. Multivariate logistic regression analysis was performed to assess the factors associated with HFNC therapy outcome. Adjusted odds ratio and 95% confidence interval (CI) were reported. Receiver operating characteristic (ROC) curves were performed and areas under the curves (AUCs) were calculated to evaluate variables for differentiating patients who will succeed or fail HFNC therapy. AUC values were analyzed using the DeLong statistical test. Cutoff values that best discriminate between HFNC success and failure was chosen to maximize the sum of sensitivity and specificity. Kaplan–Meier curves were used to determine the probability of HFNC failure/success at follow-up time intervals. These curves were compared using the log-rank test. Statistical analyses were performed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Sixty-seven patients with COVID-19 and with severe hypoxemia were initially treated with HFNC in the ED [Figure 1]. Baseline characteristics of the patients' population are presented in Table 1. Nineteen patients (28.4%) were categorized as HFNC therapy success, while the remaining 48 patients (71.6%) required escalation of respiratory support to either NIV or intubation and MV in the ED and were categorized as HFNC failure. There were no statistically significant differences in baseline characteristics among patients who succeeded or failed HFNC therapy [Table 1].

Table 1: Demographics and baseline characteristics

Variable	HFNC success (*n*=19)	HFNC failure (*n*=48)	*P*
Age, median (IQR)	65 (53–70)	70 (60–76)	0.079
Gender (female/male)	4/15	12/36	0.501
Height (cm)	171.7±10.4	171.1±9.4	0.840
Weight (kg)	92.1±20.1	86.0±19.9	0.289
Heart rate (b/min)	92.7±14.9	97.2±18.7	0.360
SpO_2 (%)	87.3±13.9	84.2±11.0	0.339
RR (br/min)	24±5	26±7	0.372
Glomerular filtration rate	77.2±26.5	72.6±29.9	0.560
D-dimer (ng/mL)	605 (328–2948)	903 (649–2780)	0.078
Procalcitonin (ng/mL)	0.17 (0.08–0.33)	0.21 (0.15–0.52)	0.079
CRP (mg/L)	54 (27–136)	145 (58–244)	0.053
Lactate (mmol/L)	1.9 (1.5–2.4)	1.9 (1.4–2.7)	0.857
PaO_2/FiO_2	75.6±20.8	66.0±15.7	0.280
Comorbidities, *n* (%)			
CHF	0	3 (6.7)	0.357
CRF	1 (5.6)	7 (15.6)	0.267
CresF	0	4 (8.9)	0.250
PSI	78 (67–98)	85.5 (70–118)	0.128
APACHE-II	9 (7.5–11)	11 (9–15.3)	0.071
SOFA	2 (2–2)	2 (2–3)	0.052

Data are presented as mean±SD, median (IQR), or *n* (%). SpO_2: Oxygen saturation by pulse oximetry, RR: Respiratory rate, PaO_2: Partial pressure of arterial oxygen, FiO_2: Fraction of inspired oxygen, CHF: Chronic heart failure, CRF: Chronic renal failure, CRespF: Chronic respiratory failure, PSI: Pneumonia severity score, APACHE-II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential organ failure assessment, IQR: Interquartile range, HFNC: High-flow nasal cannula, CRP: C-reactive protein, SD: Standard deviation

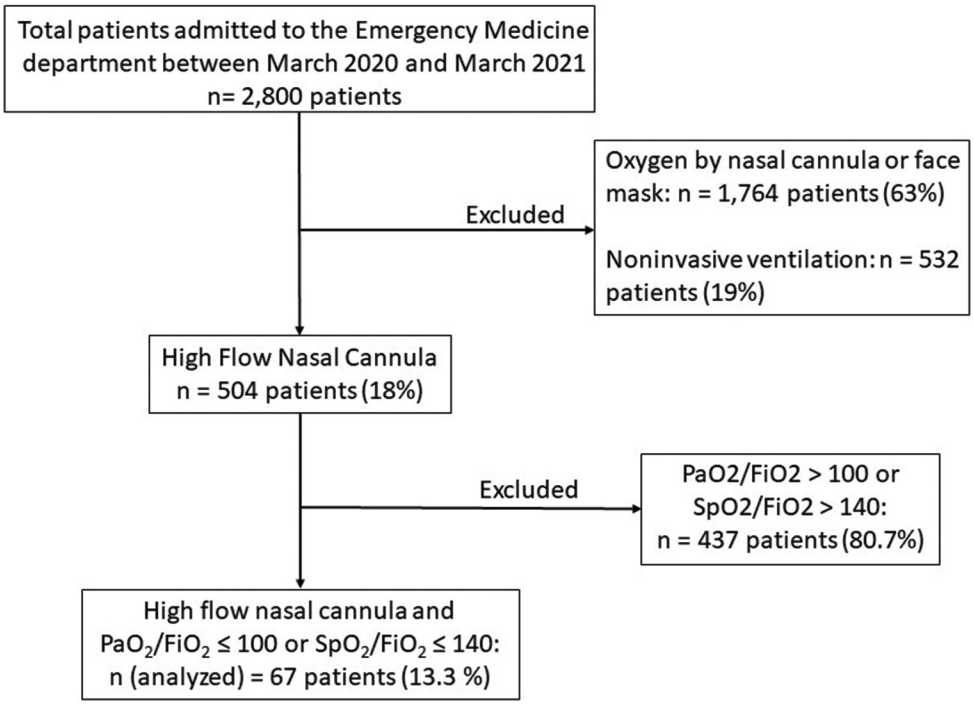

Figure 1: Study flowchart. PaO_2: Partial pressure of arterial oxygen, FiO_2: Fraction of inspired oxygen, SpO_2: Oxygen saturation by pulse oximetry

Patients with successful HFNC therapy had significantly higher SpO_2/FiO_2 at 12 h, lower RR at 6 h, and higher ROX values at 6 and 24 h of HFNC onset [Table 2]. The areas under the ROC curve (AUROCs) predicting the accuracy of SpO_2/FiO_2, RR, and ROX at different time intervals after the onset of HFNC are presented in Table 3. Only the ROX index determined at 6 and 24 h after the onset of HFNC had clinically significant predictive capacity (AUROC ≥0.7) for HFNC success/failure [Table 3]. However, the ROX index after 6 h of HFNC treatment demonstrated the best prediction accuracy with AUROC of 0.78 (95% CI: 0.66–0.90) compared to AUROC of 0.71 (95% CI: 0.54–0.89) at 24 h of HFNC treatment.

The best cutoff threshold for the ROX index at 6 h of HFNC onset was estimated to be 4.40. A ROX index ≤4.40 at 6 h after HFNC onset had a sensitivity of 71%, a specificity of 76%, a positive predictive value of 88.6%, a negative predictive value of 50%, a positive likelihood ratio of 3.0, and a negative likelihood ratio of 0.4 in predicting HFNC therapy failure. The unadjusted and confounder-adjusted odds ratios for HFNC success (i.e., no need for NIV/IMV) when ROX >4.4 were 7.8 (95% CI [2.1–28.3]) and 5.2 (95% CI [1.0–28.2]), respectively.

The follow-up time on patients was 45.78 ± 67.14 h. The median (IQR) duration of HFNC therapy was 1 (1–2) days in patients who failed HFNC compared to 1 (1–5) days in patients who succeeded HFNC therapy (P = 0.135). The median time for HFNC treatment

Table 2: Respiratory variables during high-flow nasal cannula treatment

Variable	Time (h)	HFNC success (*n*=19)	HFNC failure (*n*=48)	Effect size*	*P*
SpO_2/FiO_2	2	94±4	92±5	0.16	0.125
	6	95±4	93±4	0.24	0.065
	12	95±4	92±4	0.27	0.027
	24	94±3	92±4	0.28	0.065
RR (br/min)	2	22 (20–24)	24 (20–27)	0.17	0.162
	6	20 (20–22)	24 (20–28)	0.38	0.002
	12	20 (18–25)	22 (20–27)	0.22	0.107
	24	22 (18–20)	20 (20–27)	0.28	0.072
ROX index	2	4.3±0.7	3.9±0.9	0.18	0.148
	6	4.6±0.6	3.8±0.7	0.43	<0.001
	12	4.5±0.8	3.9±0.9	0.24	0.081
	24	4.8±0.9	4.2±0.8	0.34	0.048

*The effect size for nonparametric data; measured using the formula: Standardized test statistic/sqrt (*n*). Data are presented as mean±SD or median (IQR). SpO_2: Oxygen saturation by pulse oximetry, RR: Respiratory rate, FiO_2: Fraction of inspired oxygen, ROX: (SpO_2/FiO_2)/RR, SD: Standard deviation, IQR: Interquartile range, HFNC: High-flow nasal cannula

without the need for NIV or intubation and MV was significantly higher in patients whose ROX score was >4.4 at 6 h post-HFNC initiation compared to patients with ROX score ≤4.4 (48 h, 95% CI [7.8–88.1] vs. 24 h, 95% CI [15.8–32.2] respectively; P = 0.016).

Kaplan–Meier plots showing the probability of HFNC success according to the ROX group are shown in Figure 2. Patients with ROX index >4.4 after 6 h of HFNC were less likely to need NIV or intubation and MV (P = 0.016).

Table 3: Diagnostic accuracy of respiratory variables at different time points of need for NIV or mechanical ventilation in patients treated with high-flow nasal cannula

Variable	Time (h)	AUROC	95% CI	*P*
SpO_2/FiO_2	2	0.6	0.45–0.76	0.202
	6	0.66	0.50–0.82	0.058
	12	0.67	0.52–0.82	0.045
	24	0.68	0.51–0.84	0.073
RR (br/min)	2	0.39	0.25–0.53	0.162
	6	0.26	0.13–0.38	0.002
	12	0.36	0.21–0.52	0.107
	24	0.33	0.15–0.52	0.072
ROX index	2	0.61	0.47–0.76	0.155
	6	0.78	0.66–0.90	0.001
	12	0.65	0.50–0.81	0.071
	24	0.71	0.54–0.89	0.029

SpO_2: Oxygen saturation by pulse oximetry, FiO_2: Fraction of inspired oxygen, RR: Respiratory rate, ROX: (SpO_2/FiO_2)/RR, CI: Confidence interval, AUROC: Areas under the receiver operating characteristics curve

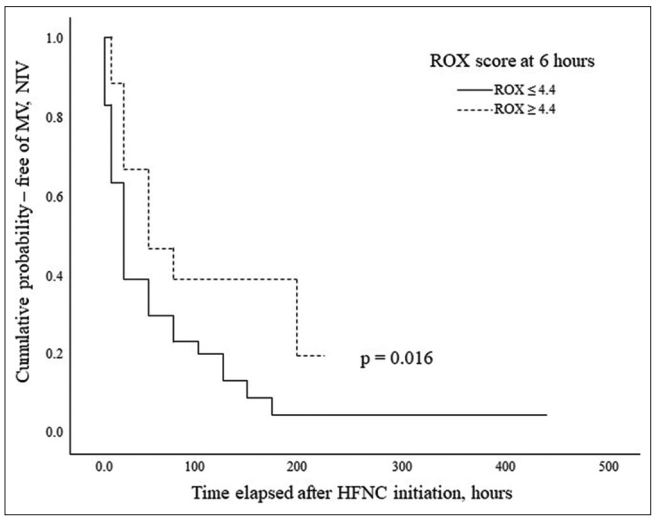

Figure 2: Kaplan–Meier plot showing the cumulative probability of remaining free of either noninvasive ventilation or intubation and mechanical ventilation in patients with COVID-19 and severe hypoxemia treated with HFNC therapy in the emergency department. HFNC: High-flow nasal cannula, MV: Mechanical ventilation, ROX: Ratio of oxygen saturation, NIV: Noninvasive ventilation

Discussion

We showed that the ROX index determined at 6 h from the onset of HFNC therapy that is >4.4 is a good predictor of HFNC success/failure in COVID-19 patients with severe hypoxemia treated in the ED.

During the COVID-19 pandemic, HFNC was feasible in treating patients with AHRF due to COVID-19 in ICU and non-ICU settings.[10,11] To date, there is a lack of robust data from randomized controlled trials (RCTs) on the timely use of HFNC in COVID-19-associated AHRF as it is hard to conduct such RCTs during a pandemic. Nevertheless, several studies have reported important clinical benefits of HFNC in COVID-19 patients and the potential role of the ROX index in predicting the outcome of HFNC.[12,13] However, none of these studies focused on a cohort group of patients with severe hypoxemia (i.e., $PaO_2/FiO_2 \leq 100$) who were managed exclusively in ED. Hu *et al*. showed in COVID-19 patients receiving HFNC in specialized respiratory units that ROX >5.5 after 6 h of HFNC therapy is a good predictor of HFNC success.[12] Although our findings are similar, there remain several important differences between the two studies. First, in Hu *et al*. study, patients were managed in specialized respiratory units while our patients were managed exclusively in the ED. Second, the median (interquartile) PaO_2/FiO_2 ratio for patients in Hu *et al*. study was 116 (102.1–132.0) compared to 64.5 (57.3–75) in the current study. As such and as per the Berlin definition of acute respiratory distress syndrome,[14] the patients in Hu *et al*. study can be classified as moderate AHRF while ours are severe AHRF.[12] Third, in Hu *et al*. study, the ROX index >5.55 at 6 h of HFNC therapy was associated with HFNC success, while in the current study, the ROX index >4.4 was associated with HFNC success. Finally, the rate of HFNC failure was higher in the current study compared to Hu *et al*. study (71.6% vs. 38.1%, respectively). The higher failure rate could be attributed to the higher severity of hypoxemia in our patients. Recently, Costa *et al*. reported a similar high HFNC failure rate of 69.6% in COVID-19 patients with severe hypoxemia.[14]

Identifying a reliable and easy-to-use predictor of the success/failure of HFNC is of great importance. It provides not only an objective index on which to base critical interventions and decisions such as termination of unduly HFNC therapy and escalation to intubation and MV but also specifies a cutoff value to use throughout the process. Unnecessary delays in intubation and initiation of MV might increase mortality in patients receiving HFNC therapy.[15] Subsequently, the identification of patients who can be maintained on HFNC therapy without being exposed to unnecessary risks and with the intention of improving their outcomes is paramount. However, close attention should be made on how, when, and what threshold to use when applying the ROX index during HFNC therapy. Several studies on using HFNC as first-line treatment at different locations in the hospital and for different patient's populations reported different ROX cutoff values ranging from 4.94 to 5.99.[12-14] However, ROX thresholds as high as 11.17 and as low as 3.0 were reported in COVID-19 patients who received HFNC therapy after liberation from MV.[15,16] These findings suggest that despite the feasibility of ROX in predicting HFNC outcome, no single ROX value is appropriate and thus different ROX values should be used at specific time intervals for different patients' categories at different locations in the hospital. In the current study, we suggest using an ROX threshold of

4.4 at 6 h from HFNC onset in COVID-19 patients with severe hypoxemia receiving HFNC in the ED.

HFNC could be a valuable and feasible treatment option for patients with COVID-19 since its easy setup allows for rapid training even for nonexpert clinicians with heterogeneous backgrounds.[1,2,12-14] Thus, its implementation in a non-ICU setting such as in ED is crucial for countries and health-care systems with shrinking critical care capacities and resources for invasive MV. Our patients were COVID-19 patients who received HFNC as an initial form of respiratory support in the ED. HFNC failure rate was 71.6% and is probably the highest HFNC failure rate reported in the literature.[2,7,12-14] However, our patients' cohort could be considered the sickest cohort with the most severe form of AHRF with a median (IQR) PaO_2/FiO_2 of 64.5 (57.3–75). Nevertheless, the current study provides valuable information for the management of COVID-19 patients in ED. First, 28.4% of COVID-19 patients with severe AHRF were successfully managed with HFNC in ED. Second, a simple ROX measured as early as 6 h after HFNC onset may be used to identify COVID-19 patients with severe AHRF who will succeed/fail HFNC therapy in ED so that HFNC is either maintained or patients are escalated to NIV or invasive MV.

In our patients, the median duration of HFNC was 1 day for both HFNC success and failure groups with no statistical difference. However, when ROX was >4.4 at 6 h from HFNC onset, the median time of HFNC without the need for either NIV or intubation and MV was significantly increased to 48 h. This suggests that in COVID-19 patients with severe AHRF, ROX >4.4 at 6 h from HFNC onset is valuable in identifying patients who will tolerate an additional day without failing HFNC in ED.

Limitations

The current study has some limitations. First, this was a single-center study and as such the current findings might not be generalized to other clinical settings; nevertheless, our findings should help in providing guidance for possible implementation at other health-care facilities. Second, the number of patients was not large enough (only 67 patients) and based on a convenient sample approach of selected COVID-19 patients who presented to our ED between March 2020 and March 2021 with a $PaO_2/FiO_2 \leq 100$. However, despite the relatively small number, this group of patients represents a unique cohort of patients with the most severe forms of AHRF ($PaO_2/FiO_2 \leq 100$) who are usually immediately intubated and started on invasive MV upon presentation to the ED or at least given a very short trial of NIV to save them from intubation and MV. To our knowledge, very few, if any, studies have reported findings on such a cohort group of COVID-19 patients with severe AHRF who received HFNC therapy as the first line of intervention for severe hypoxemia. Third, the transition from HFNC to NIV or IMV was decided by the medical team. Different ED physicians have different opinions on the criteria for terminating HFNC and switching to NIV or IMV. However, this study can still reflect on how HFNC was actually used in ED for COVID-19 patients. Fourth, since we included COVID-19 patients with only severe AHRF, our identified ROX of 4.4 cannot be generalized and used in COVID-19 patients with mild or moderate AHRF. Fifth, despite no statistically significant difference in the frequency of comorbidities between the success and failure groups, the low sample size might have masked a possible effect of lower comorbidities in the success group. This can be further evaluated with a study with larger group of patients. Finally, the ROX index was determined at specified and discrete time intervals after HFNC onset (i.e., 2, 6, 12, and 24 h), while HFNC failure may occur at any point in time. Nevertheless, previous studies have shown that the median duration of HFNC treatment in patients with AHRF was at least 24 h and hence most patients may be assessed with ROX index at the currently specified time intervals.[17]

Conclusion

Our study assessed the use of HFNC therapy in a homogenous cohort of COVID-19 patients with severe AHRF treated in ED. ROX index >4.4 at 6 h after HFNC initiation had a good predictive ability for HFNC therapy success in the ED.

Author contributions

All authors had full access to the data, contributed to the study, reviewed, edited, and approved the final version for publication, and were responsible for its accuracy and integrity.

Conflicts of interest

None Declared.

Ethical approval

This study was approved by the Institutional Review Board at the American University of Beirut, Beirut, Lebanon (IRB# BIO-2021-0318). IRB approval date: November 25, 2021.

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