Utility and timing of the respiratory rate-oxygenation index in the prediction of high-flow oxygen therapy failure in acute hypoxemic respiratory failure of infective etiology: a prospective observational study

Pramod Chaudhari,[1] Pawan Kumar Singh,[1] Manjunath Govindagoudar,[1] Vinod Sharma,[1] Puneet Saxena,[2] Aman Ahuja,[1] Lokesh Lalwani,[3] Dhruva Chaudhry[3]

[1]Department of Pulmonary and Critical Care Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana; [2]Respiratory Medicine, Research and Referral Army Hospital, New Delhi; [3]Respiratory Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

Correspondence: Dhruva Chaudhry, Respiratory Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, 124001 Rohtak, Haryana, India.
Tel.: +91.999.110-1616.
E-mail: dhruvachaudhry@yahoo.co.in

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Abstract

During and following the COVID-19 pandemic, the world has witnessed a surge in high-flow oxygen therapy (HFOT) use. The ability to provide high oxygenation levels with remarkable comfort levels has been the grounds for the same. Despite the advantages, delays in intubation leading to poor overall outcomes have been noticed in subgroups of patients on HFOT. The respiratory rate-oxygenation (ROX) index has been proposed to be a useful indicator to predict HFOT success. In this study, we have examined the utility of the ROX index prospectively in cases of acute hypoxemic respiratory failure (AHRF) due to infective etiologies. A total of 70 participants were screened, and 55 were recruited for the study. The majority of participants were males (56.4%), with diabetes mellitus being the most common comorbidity (29.1%). The mean age of the study subjects was 46.27±15.6 years. COVID-19 (70.9%) was the most common etiology for AHRF, followed by scrub typhus (21.8%). 19 (34.5%) experienced HFOT failure, and 9 (16.4%) subjects died during the study period. Demographic characteristics did not differ between either of the two groups (HFOT success *versus* failure and survived group *versus* expired group). The ROX index was significantly different between the HFOT success *versus* failure group at baseline, 2, 4, 6, 12, and 24 hours. The best cut-offs of the ROX index at baseline and 2 hours were 4.4 (sensitivity 91.7%, specificity 86.7%) and 4.3 (sensitivity 94.4% and specificity 86.7%), respectively. The ROX index was found to be an efficient tool in predicting HFOT failure in cases of AHRF with infective etiology.

Introduction

High-flow oxygen therapy (HFOT) has become a novel respiratory support mode. The COVID-19 pandemic witnessed a growing interest in the non-invasive management of acute hypoxemic respiratory failure (AHRF), fueled by the advent of HFOT [1]. Recent data shows that HFOT is associated with reduced mortality, higher ventilator-free days, and a lower risk for intubation when compared with non-invasive ventilation (NIV) in patients

with partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤200 and in those who were immunocompromised [2,3]. However, the mortality benefits of NIV have not been replicated in other studies [4].

Numerous studies have demonstrated that HFOT produces pharyngeal pressures of 2-8 cm H_2O, and it is hypothesized that these pressures may contribute to lung recruitment and splinting of the openings of the upper airways. Additionally, HFOT has been shown to provide a dead space washout of the nasopharynx and reduce the work of breathing by decreasing inspiratory resistance. Pulmonary compliance and conductance are also maintained by providing heated and humidified oxygen therapy [5-7]. Due to a false sense of patient stability and the common fear of intubation, a major consequence of the increasing use of HFOT is the risk of delayed intubation [8] and subsequent worse outcomes. This has been convincingly shown with both NIV [9], and HFOT [10], especially in patients treated for pneumonia [11]. Therefore, describing clinical variables that could be easily used at the bedside to help identify high-risk cases for intubation in a timely fashion is a task of special interest.

To address this unmet need, we planned to study the noninvasively measured bedside respiratory rate-oxygenation (ROX) index, defined as the ratio of oxygen saturation by pulse oximeter divided by the FiO_2 to respiratory rate (RR). As a predictor of eventual intubation, the ROX index individually outperformed the 2-component variables [oxygen saturation (SpO_2)/FiO_2 and RR]. Patients with a ROX index ≥4.88 after 12 hours of HFOT therapy were less likely to be intubated, even after adjusting for potential covariates [12].

Infections are the most common underlying etiological diagnosis in acute respiratory distress syndrome (ARDS) and are associated with higher mortality than other causes [13,14]. Therefore, we conducted a study to validate the ROX index's diagnostic accuracy in ARDS of infective etiology in an Indian setting to determine which patients will succeed and which will fail on HFOT and to determine the optimum ROX cut-off for Indian patients.

Materials and Methods

Design and setting

This study was conducted in the intensive care unit (ICU) of the Department of Pulmonary and Critical Care Medicine at a tertiary care teaching hospital in north India. The study was a hospital-based prospective observational study, conducted from September 2020 to December 2021. The Institutional Review Board-approved study protocol was also cleared by the Biomedical Research Ethics Committee of the Institute *via* approval letter number BREC/Th/20/02, dated September 2, 2020. The study's primary objective was to validate the existing cut-off of the ROX index (4.88) to predict HFOT failure in ARDS of infective etiology.

Participants

All patients diagnosed with AHRF defined as per the Kigali modification of the Berlin definition of ARDS defined using a pulse oximeter (SpO_2/FiO_2 <315), above the age of 18 years, and admitted to the ICU were screened for eligibility. All participants were explained the study procedures, and willingness was sought in the form of informed consent. Patients who were in immediate need of intubation, had coexistent cardiogenic pulmonary edema, hypercapnic respiratory failure, or were suffering from any malignancy were excluded from the study. Also, patients requiring hemodialysis for renal insufficiency or immunocompromised patients were excluded. The main contraindications of HFOT included hemodynamic instability, a poor sensorium, and nasal deformities.

High-flow oxygen therapy device and application

HFOT was provided using Bellavista® 1000 ICU ventilators (Bellavista Medical AG, Rüti, Switzerland) along with NICE® 8010 respiratory humidifier devices (NICE Neotech Medical Systems Pvt. Ltd., Chennai, Tamil Nadu, India) and a low-resistance Optiflow® adult nasal cannula (Fisher & Paykel Healthcare, Auckland, New Zealand), which can deliver up to 60L/min of conditioned (37°C and 100% relative humidity) gas admixture. HFOT was initiated at FiO_2 >40% and a flow of 30 L/min, titrating upwards, if tolerated, to 45-60 L/min. Subsequently, FiO_2 was adjusted to maintain oxygen saturation by a pulse oximeter (SpO_2) of 92% or more, and then the flow rate was set according to the patient's comfort, tolerance, and physician judgment. Patient positioning and proning were left at the discretion of the treating physician.

Respiratory rate-oxygenation index calculation

The parameters used to assess respiratory failure were RR, SpO_2/FiO_2 ratio, and ROX index. The ROX index was calculated at prespecified intervals: baseline, 2, 4, 6, 12, and 24 hours after starting HFOT, and at corresponding time points, patients were assessed for HFOT failure. HFOT failure was defined as the subsequent need for invasive mechanical ventilation or death, whichever was earlier. There was a predefined set of intubation criteria to help the attending physicians decide when to intubate. Predefined criteria included a deteriorating level of consciousness (Glasgow coma score <12), cardiac arrest/arrhythmias, severe hemodynamic instability (requiring norepinephrine >0.1µg/kg/min after volume resuscitation), or worsening respiratory condition defined as at least two of the following criteria: failure to achieve optimum oxygenation (PaO_2 <60 mmHg or SpO_2 <90% despite HFOT flow ≥30 L/min and FiO_2 of 1), respiratory acidosis (partial pressure of arterial carbon dioxide >50 mmHg with or without pH<7.25), RR>30 breaths/min or inability to clear secretions, or paradoxical breathing.

Statistical analysis

All patients' demographic data (age, gender), addiction history (smoking, alcohol), comorbidity (diabetes mellitus, hypertension), disease-specific clinical history (etiology of respiratory failure), monitoring details (RR, oxygen saturation by pulse oximeter, oxygen requirement, SpO_2/FiO_2 ratio, and ROX index) at baseline and also 2, 4, 6, 12, and 24 hours after the application of HFOT were recorded in case record form (paper format).

Data was later entered into Microsoft® Excel version 365 (Microsoft, Redmond, WA, USA). Before analysis, the data was curated, coded, and cleaned. The missing data was left blank. Final statistical analysis was done using SPSS® (Statistical Package for Social Sciences, IBM, Armonk, NY, USA) Version 26. Quantitative variables were expressed as mean and standard deviation or median and interquartile range per the normality criteria and tested with the Kolmogorov-Smirnov test. 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. Comparisons between categorical

variables were made using the Chi-square or Fisher exact test, as appropriate. To calculate the diagnostic accuracies of different variables for correctly identifying the study outcomes, receiver operating characteristic curves (ROC) were generated, and the area under the curves (AUROC) was calculated. The optimal threshold of continuous variables was chosen to maximize the sum of sensitivity and specificity using Youden's index. According to the cut-off points described in the ROC curve analysis for the ROX index, Kaplan-Meier curves were used to determine the probability of intubation for patients with a higher ROX index and those with a lower ROX index. These curves were compared using the log-rank test. Cox's proportional hazards modeling was chosen to identify if the ROX index was associated with a higher need for mechanical ventilation while simultaneously adjusting for other demographics and independent covariates. In addition to deriving indigenous cut-off values for the ROX index, we used the previously defined cut-off point of 4.88 described by Roca *et al.* [12]. Finally, we investigated a new cut-off value for the ROX index with the highest specificity for predicting the risk of HFOT failure. Differences in the values of the ROX index at different time points between patients who succeeded and those who failed on HFOT were also derived. A 2-sided p value of 0.05 or less was considered statistically significant.

Results

Over 15 months, 70 naïve cases of AHRF patients due to any infective cause were assessed for eligibility, out of which 8 were excluded due to the need for immediate intubation and 7 were excluded for other reasons (Figure 1). 55 patients who received HFOT were recruited in the study, and the ROX index was calculated at baseline, 2, 4, 6, 12, and 24 hours after HFOT initiation. All patients were on conventional oxygen therapy (COT) at the time of enrollment and had not received any other respiratory support for their current illness. Cases already on some other forms of respiratory support were not considered for screening.

The mean age of enrolled patients was 46.27 (±15.6) years, ranging from 19 to 80 years. Of the 55 patients, 31 (56.4%) were men, and COVID-19 was the most common cause of AHRF (70.9%). Diabetes and hypertension were present in 16 (29.1%) and 12 (21.8%) cases, respectively. 8 patients had both hypertension and diabetes mellitus. Mean SpO_2 and FiO_2 at baseline were 92.15 (±4.2) and 0.68 (±0.2), respectively. The mean SpO_2/FiO_2 ratio of the study population at baseline was 147.54 (±41.4). The mean RR at baseline was 29.67 (±2.9). The mean ROX index at baseline in the study population was 5.06 (±1.6). Detailed baseline characteristics can be found in Table 1.

HFOT was successful in 36 (65.45%) patients, whereas 19 (34.55%) patients needed intubation and mechanical ventilation (HFOT failure). 10 patients in the HFOT failure group survived after mechanical ventilation, while 9 died. Overall hospital mortality in the study population was 16.36%, while hospital mortality in the study population of AHRF due to COVID-19 was 23.07%. All 55 patients were included in the final analysis. Mean age, sex distribution, comorbidities, smoking status, and basic diagnosis were similar in the two groups of HFOT success and HFOT failure (Table 1). Among the patients who survived and among those who died during the study period, none of the baseline characteristics was different except for age [mean age was

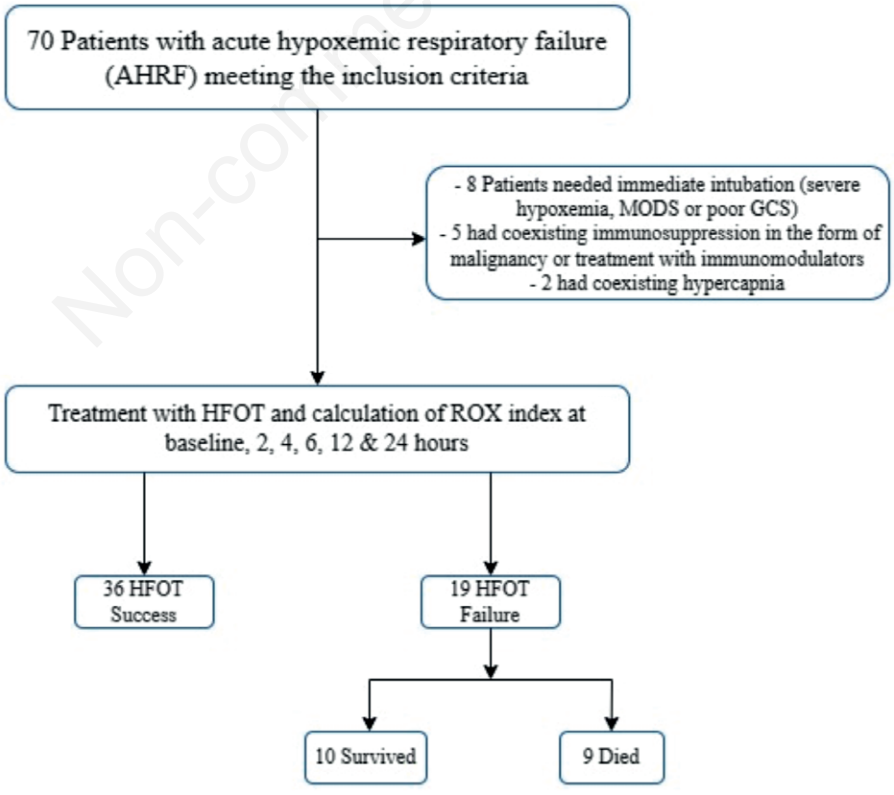

Figure 1. Consort diagram of the study. HFOT, high-flow oxygen therapy; ROX, respiratory rate-oxygenation; MODS, multiorgan dysfunction syndrome; GCS, Glasgow coma scale.

44.33 (±15.36) years in the survivor group *versus* 56.22 (±13.71) years in the expired patients' group (p<0.05)] and etiology (65.21% of patients in the surviving population suffered from COVID-19, while all patients who expired had COVID-19, p<0.05) (Table 1).

To assess the primary outcome, respiratory variables monitored serially after the initiation of HFOT treatment in the study population were significantly different between the two groups. Values of SpO_2, SpO_2/FiO_2, and ROX index were higher, whereas FiO_2 requirement and RR were significantly lower in the HFOT success group as compared to the HFOT failure group (p<0.05) (Table 2). We anticipated that HFOT flow would play a role in providing PEEP as well as dead space reduction; hence, the same was also analyzed for the outcome but was not found to be significantly different among the subgroups. The predictive accuracy of different respiratory variables for the need for MV in patients treated with HFOT in the study population was calculated using the AUROC. The predictive accuracy of the ROX index and SpO_2/FiO_2 increased over time, as observed in the form of serially increasing values of AUROC (Figure 2).

The optimum ROC cut-off values for the ROX index to predict HFOT failure (intubation) at different time points, calculated using the Youden index, are provided in Table 3. The cut-offs at baseline and 2 hours were 4.4 and 4.3, respectively. To optimize the analysis, we used a lower cut-off, which was expected to have higher sensitivity for the detection of HFOT failure.

The mean duration of the HFOT was statistically similar in the two groups [the HFOT success group was 77.33 (±41.98) hours *versus* 57.05 (±45.83) hours in the HFOT failure group, p=0.118]. Survival analysis using Kaplan-Meier plots showed significant differences in the probability of HFOT therapy success, with the derived cut-off of 4.3 at baseline, 2, 4, 6, 12, and 24 hours, as well as with the cut-off of 4.88 at baseline, 2, 4, 6, 12, and 24 hours (Kaplan-Meier curves with a cut-off at 2 hours are shown in Figure 3). Hazard ratios (HR) for intubation, for ROX index ≥4.88 and ≥4.3 at baseline and 2 hours were also calculated using Cox regression. For ROX ≥4.88 at baseline and 2 hours, HR was 0.182; 95% confidence interval (CI): 0.052, 0.637; p<0.01 and 0.091; 95% CI: 0.021, 0.395; p<0.001, respectively; and for ROX ≥4.3 at baseline and 2 hours, HR were 0.114; 95% CI: 0.033, 0.397; p<0.001 and 0.060; 95% CI: 0.014, 0.262; p<0.001, respectively.

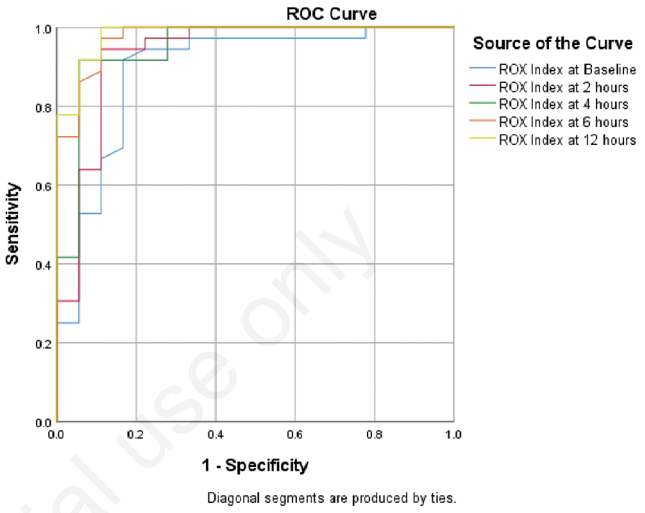

Figure 2. Receiver operator characteristic curve of respiratory rate-oxygenation index to predict high flow-oxygen therapy failure at baseline and at 2, 4, 6, and 12 hours after its initiation. ROC, receiver operator characteristic; ROX, respiratory rate-oxygenation.

Table 1. Comparison of baseline characteristics between patients who succeeded or failed high-flow oxygen therapy treatment and between patients who survived or died. Data are means ± standard deviation, median (interquartile range) or n (%).

	Total (n=55)	HFOT success (n=36)	HFOT success (n=19)	p value	Survived (n=46)	Died (n=9)	p value
Male, n (%)	31 (56.4)	22 (61.11)	9 (47.36)	0.328	27 (58.69)	4 (44.44)	0.430
Age (years) (median, IQR)	45 (36-58)	43 (38-53)	48.5 (35.25-59.50)	0.704	43 (35-55.25)	53 (44-68)	0.04
Residence (Urban) n (%)	34 (61.8)	21 (58.3)	13 (68.4)	--	28 (60.9)	6 (66.7)	--
Comorbidities, n (%)							
Diabetes mellitus	16 (29.09)	9 (25%	7 (36.84)	0.358	11 (23.91)	5 (55.56)	0.056
Hypertension	12 (21.81)	8 (22.22)	4 (21.05)	0.920	9 (19.56)	3 (33.33)	0.360
Smoking status	9 (16.36)	5 (13.88)	4 (21.05)	0.495	6 (13.04)	3 (33.33)	0.132
Etiology of AHRF, n (%)							
COVID-19	39 (70.90)	24 (66.67)	15 (78.94)	0.340	30 (65.21)	9 (100)	0.036
Scrub typhus	12 (21.81)	8 (22.22)	4 (21.05)	0.920	12 (26.08)	0 (0)	0.083
Dengue fever	2 (3.63)	2 (05.55)	0 (0)	0.295	2 (04.34)	0 (0)	0.524
Bacterial	2 (3.63)	2 (05.55)	0 (0)	0.295	2 (04.34)	0 (0)	0.524
Duration of HFOT (hours) (mean±SD)	70.33 (±32.5)	77.33 (±41.98)	57.05 (±45.83)	0.118	71.48 (±42.95)	64.44 (±51.48)	0.708
APACHE II score (mean±SD)	11.5±1.3	10±2.1	11±1.9	0.708	10±2.4	11±2.1	0.796
C-reactive protein levels in mg/L (mean±SD)	26.9±5.2	25.2±8.1	29.1±9.0	0.105	25.4±9.9	29.4±11.0	0.091

HFOT, high-flow oxygen therapy; IQR, interquartile range; APACHE, acute physiologic assessment and chronic health evaluation; SD, standard deviation.

Table 2. Respiratory variables during high-flow oxygen therapy treatment: comparing high-flow oxygen therapy success group with the failure group. Data are presented as means ± standard deviation.

Variable	Time (h)	Success (n=36)	Failure (n=19)	p-value
SpO_2	Baseline	93.58 (±2.92)	89.42 (±4.9)	0.002
	2 hours	94.50 (±2.21)	90.74 (± 3.68)	<0.001
	4 hours	94.53 (±2.10)	91.37 (±3.20)	0.001
	6 hours	94.81 (±1.65)	90.37 (±3.50)	<0.001
	12 hours	94.69 (±1.75)	90.28 (±4.25)	<0.001
	24 hours	94.69 (±1.83)	90.40 (±3.79)	0.001
FiO_2	Baseline	0.59 (±0.12)	0.84 (±0.21)	<0.001
	2 hours	0.58 (±0.11)	0.87 (±0.18)	<0.001
	4 hours	0.56 (±0.11)	0.85 (±0.18)	<0.001
	6 hours	0.53 (±0.10)	0.87 (±0.15)	<0.001
	12 hours	0.50 (±0.10)	0.86 (±0.14)	<0.001
	24 hours	0.48 (±0.10)	0.82 (±0.14)	<0.001
Flow of HFNC	Baseline	42.2 (±12.1)	46.5 (±13.8)	0.112
	2 hours	42.5 (±11.9)	46.8 (±11.0)	0.109
	4 hours	42.1 (±11.7)	45.8 (±12.6)	0.225
	6 hours	44.2 (±10.6)	45.9 (±10.2)	0.802
	12 hours	38.5 (±12.8)	44.2 (±9.1)	0.091
	24 hours	40.1 (±12.1)	45.6 (±11.2)	0.101
SpO_2/FiO_2	Baseline	164.55 (±28.68)	115.32 (±43.08)	<0.001
	2 hours	167.32 (±27.80)	112.07 (±40.76)	<0.001
	4 hours	175.76 (±30.91)	114.78 (±35.81)	<0.001
	6 hours	185.34 (±35.17)	108.69 (±27.56)	<0.001
	12 hours	197.71 (±37.59)	109.45 (±27.23)	<0.001
	24 hours	206.78 (±41.64)	113.89 (±26.68)	<0.001
RR, breaths/minute	Baseline	28.56 (±2.55)	31.79 (±2.39)	<0.001
	2 hours	26.86 (±2.65)	31.47 (±2.74)	<0.001
	4 hours	26.39 (±2.43)	30.74 (±2.51)	<0.001
	6 hours	26.00 (±2.53)	31.16 (±3.00)	<0.001
	12 hours	25.83 (±3.11)	31.00 (±2.59)	<0.001
	24 hours	24.72 (±2.62)	30.40 (±2.64)	<0.001
ROX index	Baseline	5.83 (±1.28)	3.60 (±1.17)	<0.001
	2 hours	6.33 (±1.43)	3.56 (±1.21)	<0.001
	4 hours	6.76 (±1.56)	3.75 (±1.13)	<0.001
	6 hours	7.26 (±1.86)	3.51 (±0.90)	<0.001
	12 hours	7.85 (±2.12)	3.56 (±0.92)	<0.001
	24 hours	8.55 (±2.28)	3.75 (±0.79)	<0.001

SpO_2, oxygen saturation with pulse oximetry; FiO_2, fraction of oxygen in inspired air; HFNC, high-flow nasal cannula; RR, respiratory rate; ROX, respiratory rate-oxygenation.

Table 3. Optimum receiver operator characteristic curve cut-off value for respiratory rate-oxygenation index to predict high-flow oxygen therapy failure.

Test result variable		Value	Sensitivity	Specificity
ROX index at baseline	Value with 100% sensitivity	2.74	1.000	0.200
	Value with 100% specificity	7.14	0.250	1.000
	ROC cut-off value	4.37	0.917	0.867
ROX index at 2 hours	Value with 100% sensitivity	3.46	1.000	0.667
	Value with 100% specificity	7.55	0.306	1.000
	ROC cut-off value	4.31	0.944	0.867
ROX index at 4 hours	Value with 100% sensitivity	3.95	1.000	0.733
	Value with 100% specificity	7.20	0.417	1.000
	ROC cut-off value	4.92	0.917	0.933
ROX index at 6 hours	Value with 100% sensitivity	4.28	1.000	0.800
	Value with 100% specificity	5.66	0.722	1.000
	ROC cut-off value	4.61	0.972	0.867
ROX index at 12 hours	Value with 100% sensitivity	4.33	1.000	0.867
	Value with 100% specificity	5.93	0.778	1.000
	ROC cut-off value	4.33	1.000	0.867

ROC, receiver operator characteristic; ROX, respiratory rate-oxygenation.

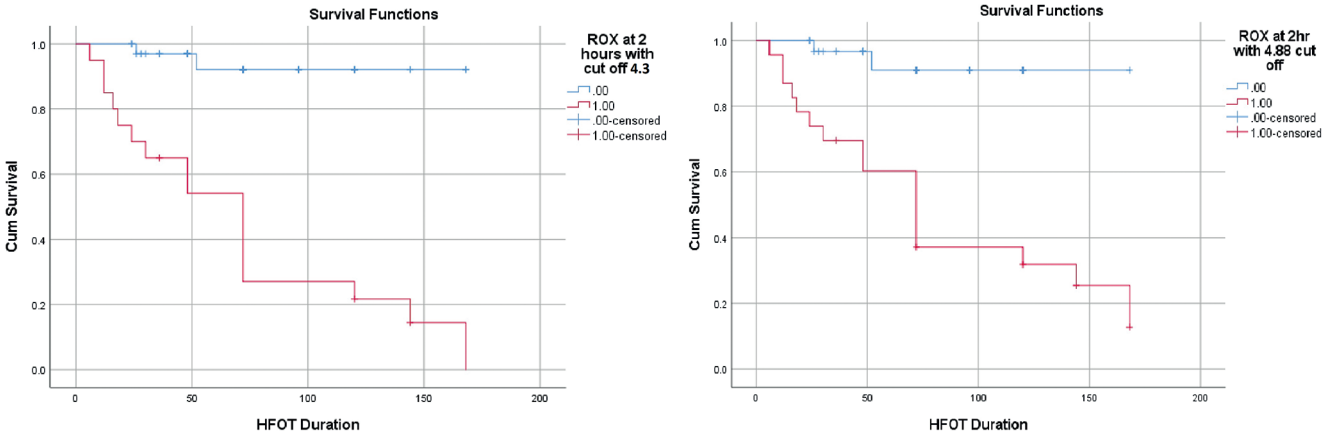

Figure 3. Survival analysis using Kaplan-Meier plots comparing differences in the probability of high-flow oxygen therapy success, with the derived cut-off of respiratory rate-oxygenation index 4.3 and 4.88 at 2 hours. HFOT, high-flow oxygen therapy; ROX, respiratory rate-oxygenation.

Discussion and Conclusions

In this study, we found that the ROX index at both values of 4.88 and 4.3 was superior to other respiratory variables in predicting the outcome of HFOT in AHRF patients of infective etiology.

In patients with respiratory failure, both acute and chronic, different kinds of respiratory supports are used to improve oxygenation as well as ventilation. Among these, high-flow nasal oxygen therapy is an emerging form of non-invasive respiratory support that is gaining popularity and attention among clinicians, especially due to its tolerance and patient comfort [15,16].

COT, *i.e.*, the administration of oxygen *via* a nasal cannula or face mask, has been considered the frontline treatment for acute and chronic hypoxemia for a long time. However, only low flows of oxygen (up to 15 L/min) can be delivered *via* a traditional cannula or mask due to insufficient heating and humidification of the inhaled gas, which causes discomfort to the patient as the flow increases [17]. In addition to COT, NIV has been extensively used and studied in respiratory failure in different settings. Despite its effectiveness, NIV is poorly tolerated by several patients due to the high pressures delivered in the airways, difficulty in synchronized breathing, claustrophobia, stomach distension due to aerophagia, and mask-related side effects such as nose sores and skin lesions over the nasal bridge [18].

HFOT is an emerging technique designed to provide oxygen at high flows with optimal heating and humidification *via* an interface consisting of a silicone cannula that fits the nose without occluding and offers better comfort, compared with NIV, and more efficient oxygenation than COT [17]. HFOT was first introduced into clinical practice in the early 2000s as a non-invasive system to manage apnea in premature neonates. Since then, its use in pediatrics, particularly for respiratory failure caused by bronchiolitis, has gradually increased. Subsequently, HFOT has been investigated in adults with acute respiratory failure, gaining increasing popularity among intensivists [19,20].

A dire consequence of the increasing use of non-invasive oxygenation strategies is the risk of delaying needed intubation, which may lead to poor outcomes. Predicting the failure of non-invasive strategies to manage AHRF to avoid delaying needed intubation is a major challenge faced by clinicians in the ICU. Consistent data indicate that "late" intubation is associated with worse outcomes in patients with acute respiratory failure [21,22]. The same has been found true in patients treated with HFOT [9]. In a retrospective study from Japan, early intubation, defined as an intubation oxygen requirement of ≤6 lpm, was evaluated for survival outcomes. The final analysis consisting of 412 cases showed that early intubation was associated with decreased in-hospital mortality among COVID-19 patients as compared to non-early intubation, with an adjusted odd ratio of 0.28 (95% CI: 0.19-0.42; p<0.001) [23].

Similarly, one of the first prospective studies evaluating the role of NIV after extubation demonstrated that delayed intubation was associated with a higher risk of mortality [24]. In contrast, a separate study showed that early intubations, defined as intubations done in the emergency department, were associated with a higher risk of mortality, confounded by a higher number of comorbidities and worse clinical severity scores [25]. Therefore, the prediction of HFOT outcomes and timing of intubation continues to be challenging. A previous study had shown that the ROX index measured 12 hours after HFOT initiation was a better predictor of treatment success than SpO_2/FiO_2 or RR alone [12]. We found that the value of the ROX index (4.88), as proposed by Roca *et al.*, holds good discriminatory power for the Indian population with AHRF of infective etiology. Additionally, we found that the cut-off of 4.3 performed similarly well in our cohort.

Despite the higher proportion of COVID-19 cases, the demographic profile of our study participants was similar to the previous studies on similar subjects [5,26-31]. A higher proportion of males, diabetes mellitus, and hypertension cases reflect the probability of developing severe diseases due to SARS-CoV-2 infections in these subgroups. HFOT duration and success rates were similar to the previous studies.

Roca *et al.* first described that a ROX index higher than 4.88 after 12 hours of HFOT treatment predicted a lower risk of intubation in pneumonia patients [12]. Most studies done during the COVID-19 pandemic studied the ROX index in COVID-19 ARDS patients. They gave variable cut-off values of ROX with time after HFOT initiation ranging from 3.67 (at 12 hours) by Chandel *et al.* [32], to 5.99 by Vega *et al.* [27]. Our study validated the discriminatory power of the ROX index value of 4.88 to predict HFOT failure. We also derived a cut-off value of 4.3, which has higher sensitivity and specificity to predict intubation at 2, 6, and 12 hours after HFOT initiation. The performance of both values was largely

similar, which can be estimated by the approximately similar HR values for both cut-offs. We anticipated that, given the dynamicity of the disease and unfavorable outcomes with delayed intubation, early prediction of HFOT failure could improve the outcomes in AHRF when this non-invasive strategy is used. Hence, we derived cut-off values at various time intervals from 2 to 12 hours and found that the performance of the ROX index remains the same, and a 12-hour waiting period is not required. This finding is similar to previous studies conducted in a cohort of pneumonia patients treated with HFOT. In our population, the sensitivity and specificity of the ROX index were superior to those demonstrated by Roca *et al*. The probable reason could have been the differences in the severity of illnesses and the differences in the underlying etiology of AHRF since most of our patients had COVID-19 pneumonia.

Nevertheless, the ROX index should not be considered in isolation when making decisions regarding intubation. Other parameters, like neurological condition, concomitant organ failures, duration of illness, and availability of trained staff, should be considered when deciding on intubating the patient.

In summary, as a first step, we tried to evaluate the early predictors of HFOT failure in ARDS of infective etiology in an Indian population. Despite the previous observations of using the time limit of 12 hours, we found that ROX index values at baseline, 2, and 4 hours had similar predictive accuracy for HFOT failure. Continuing HFOT for prolonged periods did not reduce the probability of its failure. This fact can be used as one of the factors by the treating intensivists in taking an early call on intubation. However, this is valid only when the other variables affecting the saturation parameters are considered, like fever, mobilization, acidosis, and hypotension. Despite the strengths, the index study did have some shortcomings, like being a single-center study with a relatively small sample size and a lack of measurement of traditional inflammatory biomarkers of COVID-19 like D-dimer and interleukin 6.

Given that the majority of our study population was suffering from COVID-19 ARDS, the results are prone to being biased toward COVID-19-related interpretations. Using further sample populations as validation cohorts could also have added to the study value. Finally, single ICU practices play a significant role in the overall outcome of patients.

In conclusion, we confirmed that a ROX index greater than or equal to 4.88 measured at baseline, 2, 4, or 12 hours determines HFOT success in AHRF patients, even after adjusting for potential confounders. We propose a new ROX index value of 4.3 with high discriminatory power to predict HFOT success. Also, the accuracy of the ROX index does not improve significantly when used at 12 hours instead of an early time point, reflecting its applicability to be used at 2 or 4 hours.

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