Relationship of ROX and Modified ROX index with High Flow Nasal Cannula Oxygen therapy in COVID-19 patients: An observational, pilot study

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Abstract

Background and aim: Delayed intubation and mechanical ventilation are associated with poor outcomes. High Flow Nasal Cannula (HFNC) oxygen therapy is increasingly used with variable success, including COVID-19. Early failure detection is crucial; ROX and modified ROX (mROX) index have been proposed. The present study evaluated the utility and relationship of ROX and mROX indexes in COVID-19 patients started on HFNC oxygen therapy.

Methods: the present, prospective, observational pilot study collected data from adult COVID-19 patients admitted to intensive care with acute respiratory failure and requiring HFNC oxygenation from 29 Jan - 29 Jun 2021. Clinico-demographic data related to ROX and mROX was collected and calculated. The patients were divided into two cohorts based on the HFNC therapy success, and ROX and mROX were compared as screening tools for predicting failure. Further, the area under the curve for ROX and mROX was also assessed for mean values and accuracy. Epitools and MedCalc software were used online for different statistical analyses, and $p < 0.05$ was considered statistically significant.

Results: Twenty-seven out of 32 patients during the observation period fulfilled inclusion criteria; 13 (48.15%) of the HFNC oxygenation therapy failed. The majority (74.1%) of the patients were male; the cohort's mean $\pm$ standard deviation age was 53.93 $\pm$ 10.67 years. Both mean ROX and mROX at admission and six-hour time-point showed fair-to-good sensitivity and specificity; the accuracies for predicting failure for ROX versus mROX at baseline values 4.78 and 3.98, and six-hour values of 4.5 and 4.05 were 59.81 versus 70.68, and 67.42 versus 74.88 respectively (all $p > 0.05$). Only mROX of 4.05 (mean value) and 3.34 (Youden's J cut-off) had a sensitivity plus specificity at 1.56 and 1.63 (i.e., 156% and 163%), respectively. The mROX values between HFNC success and failure at baseline and six hours differed significantly. However, the area under the ROC for ROX and mROX at baseline and six hours were statistically indifferent.

Conclusion: Both ROX and mROX at baseline and six hours had fair-to-good sensitivity, specificity, positive and negative predictive values, and area under the ROC; the differences were statistically insignificant. The accuracies of the indices were better at six hours than the baseline. Although both the indices can be used, only mROX of 4.05 at six-hour had a sensitivity plus specificity of 156% to be considered a clinically valuable screener.

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Introduction

Severe acute respiratory syndrome following Coronavirus disease of 2019 (COVID-19) has been a global pandemic for nearly two and a half years [1]. These patients are often hypoxemic and need oxygen supplementation. High flow nasal cannula (HFNC) O_2 therapy is one of the newer yet commonly used in critical care during acute hypoxemic respiratory failure (AHRF). The World Health Organization and other scientific societies list HFNC O_2 among the possible options for ventilatory support. A recent systemic

review indicates that HFNC O_2 therapy may reduce the need for invasive ventilation and escalation of therapy compared with conventional oxygen therapy in COVID-19 patients with AHRF [2]. Also, in their recent guidelines on the management of critically ill adults with COVID-19, the Surviving sepsis campaign recommends using HFNC over non-invasive positive pressure ventilation (NIPPV) [3].

However, HFNC Oxygenation might delay identifying the need for intubation that would have become necessary. This delay seems to be associated with a poorer prognosis [4]. Roca et al. have formulated and subsequently validated the diagnostic accuracy of an index (termed ROX and defined as the ratio of SpO_2/FiO_2 to respiratory rate) for determining HFNC failure. They demonstrated that the ROX index could assist the clinician in deciding whether or not to intubate patients on HFNC O_2 therapy for AHRF [5].

On the other hand, it has been seen that the respiratory rate of patients with COVID-19-related AHRF is sometimes lower than those with other AHRF due to other common causes, which can be attributed to the severe level of hypoxia associated with it. As the ROX index uses respiratory rate as the denominator, the ROX index threshold for predicting HFNC O_2 therapy failure may be different in the case of COVID-19-associated AHRF. Further, in some patients with COVID-19, the phenomenon of "Happy Hypoxia," or more correctly, "Silent Hypoxia," has been seen [6]. Such patients exhibit shallow oxygen levels (demonstrated by pulse oximetry values) but do not demonstrate dyspnoea, irritability, or other signs of hypoxia. Furthermore, while the SpO_2/FiO_2 has a good correlation with PaO_2/FiO_2 with low concentrations of supplemental oxygen [7], whether this relationship stands well in patients receiving FiO2 of 100% is not well established. Nevertheless, the correlation of SpO_2/FiO_2 with PaO_2/FiO_2 and the fall of SpO_2 with PaO_2 is not linear [8, 9].

As SpO_2 is also used as one of the parameters for calculating the ROX index, the accuracy of the ROX index thresholds in predicting HFNC failure in COVID-19 patients might have to be validated again. A relevant modification of the said index has been proposed by Karim et al., termed the "Modified ROX (mROX) index" [10]. The mROX has proposed using PaO_2 in place of SpO2 to calculate the index. The present prospective, observational pilot study was aimed to evaluate the relationship of ROX and mROX index for predicting failure of HFNC O_2 therapy in COVID-19 patients with AHRF.

Material & Methods

The present observational pilot study was conducted in a tertiary care teaching and research institute. The data collection was done between 29 Jan 2021 to 29 Jun 2021. The research protocol was reviewed by the research cell and approved by the institutional ethical committee, and subsequently was registered in the clinical trial registry of India prospectively. The study follows the declaration of Helsinki and the Good Clinical Practice Guideline for biomedical research. The study result is reported as per the STROBE guideline.

Patients admitted with COVID-19 infection requiring intensive care management and on HFNC oxygen therapy for oxygen supplementation were screened for enrolment. The inclusion criteria were patients

aged 18–70 years on HFNC oxygen therapy with continuous SpO_2 and RR monitoring. Patients with known pre-existing respiratory diseases like COPD, Bronchial Asthma, idiopathic pulmonary fibrosis, active cardiac diseases, and chronic renal failure with pulmonary edema were excluded. The sample size was calculated using an online sample size calculator https://www.crutzen.net/n.htm. [11] We hypothesized a 10% probability of finding a difference between the ROX and mROX and considered a 95% confidence, resulting in a sample size of 29 patients.

Data were collected by observing the patients' parameters from the multiparameter monitor, patients' files, and reports. The investigating team did not intervene in any phase of the treatment of the patients. All patients were on continuous peripheral oxyhemoglobin saturation (SpO_2) monitoring; arterial blood gas (ABG) analysis was often done to assess the progress of the artificial respiratory support and escalation-de-escalation of support. All patients put on HFNC O_2 therapy were approached for recruitment and only consented patients were enrolled. Over and above demographic and history of illness related data; respiratory rate (RR), SpO_2, and the fraction of inspired O_2 (FiO_2) data were collected every six hours till the patient was either weaned from HFNC or therapy was converted to NIPPV (Bi-level) or invasive mechanical ventilation (IVM). RR, SpO_2, and FiO_2 data were also collected whenever the treating team collected an ABG sample. Further, when the treating team decided to intubate or escalate from HFNC, considering it a failure, RR, SpO_2, FiO_2, and ABG data were collected at that time point too. ROX and mROX index values were calculated from these data. HFNC failure was defined as the need for either NIV (Bi-level) or IMV as decided by the attending physician. Usually, decreased level of consciousness (Glasgow coma score < 12), cardiac arrest/arrhythmias, and severe hemodynamic instability requiring (norepinephrine > 0.1µg/kg/min) or persisting or worsening respiratory conditions are defined as at least two of the following criteria: failure to achieve adequate oxygenation (PaO_2 < 60mmHg or SpO_2 < 90% despite HFNC flow ≥ 60L/min and FIO_2 of 100%), respiratory acidosis ($PaCO_2$ > 55 mmHg or with pH < 7.25), RR > 30/min or inability to clear secretions were the factors considered for determining the failure. However, a strict protocol for adherence was absent, but the investigating team noted these criteria-related data at the failure time-point. The disease severity was assessed by acute physiology, chronic health evaluation II (APACHE II) score at 24 hours, and organ failure by sequential organ failure assessment (SOFA).

Continuous variables are reported as mean ± standard deviation (SD) or median [interquartile range (IQR)] when appropriate. The differences between the two groups were analyzed by Student’s t-test or Mann–Whitney U test. Categorical variables are reported as numbers and percentages and analyzed using the Fisher's exact or Chi-square test. INSTAT software (Graphpad Prism software Inc; La Jolla, CA, USA) was used for this analysis. The receiver operating characteristic (ROC) curves and Youden’s J point analysis were done online using Epitools-Epidemiological Calculators (https://epitools.ausvet.com.au/). Diagnostic test evaluation statistical tests for accuracies were done using MedCalc (https://www.medcalc.org/) free statistical calculator online. A two-tailed p-value < 0.05 was considered significant.

Results

A total of 32 patients were screened for eligibility; one was excluded as per the age criteria, and four patients' HFNC O_2 therapy was deemed to be ineffective within a few minutes of admission. Data from the rest of the 27 patients were included for final analysis. Three-fourths of the data were from male patients. The mean ± SD age of the patients was 53.93 ± 10.67 years. The clinicodemographic data are presented in Table 1.

Table 1
Clinico-demographic data of the cohort. Note: self-reported weight and heights were also included when the measurement was not available

Parameters	All (N = 27)	Success (N = 14)	Failure (N = 13)	Two-tailed p
Age	53.93 ± 10.67	53.93 ± 11.32	53.93 ± 10.39	0.999
Male	20 (74.1)	10 (71.4)	10 (76.9)	0.948
Female	7 (25.9)	4 (28.6)	3 (23.1)	
Weight	65.63 ± 9.89	68.36 ± 9.25	62.69 ± 10.06	0.330
Height	168.44 ± 5.79	168.71 ± 6.49	168.15 ± 5.16	0.969
BMI	23.14 ± 3.46	24.13 ± 3.91	22.08 ± 2.64	0.303
Diabetes Mellitus	5 (18.52)	2 (14.29)	3 (23.1)	0.948
Hypertension	9 (33.3)	4 (28.57)	5 (38.46)	
CKD/AKI on CKD	1 (3.7)	0	1 (7.69)	
OSA/ COPD/ Asthma	3 (11.11)	1 (7.14)	2 (15.38)	
Others	4 (14.8)	2 (14.29)	2 (15.38)	

Thirteen (48.15%) out of the 27 patients' HFNC therapy failed, mostly within 6–24 hours (range 6–96 hours). In the univariate analysis, SOFA, blood urea nitrogen level at admission, ROX at six hours, and mROX at admission and six hours were significantly different among the success and failure cases (Table 2).

Table 2
Clinico-laboratorial and monitoring data of the cohorts. (APACHE: Acute Physiology and Chronic Health Evaluation, SpO_2: peripheral oxyhaemoglobin saturation, PaO_2: partial pressure of arterial Oxygen, PCO_2: partial pressure of arterial Carbon-di-oxide, CXR; chest X-ray, ROX: Respiratory rate oxygenation index, mROX: modified Respiratory rate oxygenation index.)

Parameters	All (N = 27)	Success (N = 14)	Failure (N = 13)	Two-tailed P-value
APACHE-II	8.81 + 2.38	8.28 ± 2.33	9.38 ± 2.39	0.2373
SOFA	3.51 ± 1.55	2.78 ± 0.80	4.30 ± 1.79	0.007
Glassgow Coma Scale	15 (15–15)	15 (15–15)	15 (15–15)	—
Mean Blood Pressure	94.4 ± 10.97	96.92 ± 11.80	91.69 ± 9.72	0.219
Respiratory Rate	27.29 ± 4.17	26.85 ± 3.95	27.76 ± 4.51	0.58
SpO_2	91.18 + 4.82	92.5 ± 3.79	89.76 ± 5.54	0.151
PaO_2	75.53 ± 31.51	83.71 ± 36.80	66.72 ± 22.83	0.16
PCO_2	34.01 ± 4.97	34.03 ± 4.50	33.98 ± 5.61	0.97
Blood Urea Nitrogen	20.43 ± 11.11	16 + 6.58	25.20 ± 13.16	0.03
FiO_2 at admission	0.75 ± 0.19	0.70 ± 0.21	0.82 ± 0.16	0.10
FiO_2 at six hours	0.84 ± 0.16	0.81 ± 0.16	0.88 ± 0.14	0.254
Quadrants involves in CXR	3.03 ± 0.85	2.78 ± 0.97	3.30 ± 0.63	0.11
ROX on admission	4.87 ± 1.67	5.42 ± 1.73	4.29 ± 1.44	0.07
mROX on admission	3.99 ± 1.95	4.78 ± 2.11	3.15 ± 1.38	0.02
ROX at six hours	4.50 + 1.41	5.05 ± 1.60	3.92 ± 0.90	0.033
mROX at six hours	4.05 + 2.30	5.07 ± 2.71	2.95 ± 0.98	0.01
ROX on admission versus at six hours (success)				0.563
ROX on admission versus at six hours (failure)				0.441
mROX on admission versus at six hours (success)				0.752
mROX on admission versus at six hours (failure)				0.683

The mean values of the ROX and mROX at the baseline and six hours were higher for success cases than failure; the difference was significant except for ROX at baseline (Fig. 1).

The sensitivity, specificity, accuracy, predictive values, and likelihood ratio analysis showed slightly better values for mROX at six hours. However, the differences were insignificant statistically (Table 3). At six hours, the mean mROX value was 4.05 and had the highest sensitivity of 87.5%, a positive likelihood ratio of 2.37, and sensitivity plus specificity of 156%.

Table 3
Diagnostic statistics for assessing accuracies for the indices at the mean values (Note- *mark indicates that the values were specific for HFNC failure prevalence 48.15% as of our study) (ROX: Respiratory rate oxygenation index, mROX: modified Respiratory rate oxygenation index.)

Statistic	**Value (95% Confidence Interval)**			
	ROX at admission [mean 4.78]	**mROX at admission [mean 3.98]**	**ROX at 6 hours [mean 4.5]**	**mROX at 6 hours [mean 4.05]**
Sensitivity (%)	63.64 (30.79–89.07)	75.00 (42.81–94.51)	72.73 (39.03–93.98)	87.50 (47.35–99.68)
Specificity (%)	56.25 (29.88–80.25)	66.67 (38.38–88.18)	62.50 (35.43–84.80)	63.16 (38.36–83.71)
Positive Likelihood Ratio	1.45 (0.71–2.97)	2.25 (1.02–4.94)	1.94 (0.94–4.02)	2.37 (1.25–4.52)
Negative Likelihood Ratio	0.65 (0.26–1.58)	0.38 0.13–1.06)	0.44 (0.15–1.23)	0.20 (0.03–1.28)
Positive Predictive Value (*)	57.46 (39.84–73.37)	67.63 (48.75–82.1)	64.30 (46.49–78.87)	68.80 (53.66–80.77)
Negative Predictive Value (*)	62.49 (40.54–80.27)	74.17 (50.29–89.07)	71.16 (46.66–87.44)	84.47 (45.73–97.23)
Accuracy (*)	59.81 (39.32–78.06)	70.68 (50.14–86.47)	67.42 (46.80–84.06)	74.88 (54.58–89.44)
Sensitivity + Specificity	119.85% (1.198)	141.6% (1.416)	135.2% (1.352)	150.66% (1.566)

Similarly, the area under the ROC curve was also highest for mROX at six hours, i.e., 0.81 (95% CI 0.636–0.985), while the ROX at six hours had an AUC of 0.717 (95%CI 0.512–0.92). The same for ROX baseline was 0.712 (95% CI 0.512–0.911) while for the mROX baseline was 0.747 (95% CI 0.558–0.937). The Youden's J cut-off point for ROX and mROX at baseline was 4.59, 4.1, and six hours 4.47 and 3.34, respectively. The sensitivity and specificity at Youden's J cut-off points for the ROX and mROX and their efficacy at p 0.01 and 0.05 are presented in Table 4.

Table 4
The sensitivity and specificity at Youden's J cut-off points for the ROX and mROX and their efficacy at P 0.01 and 0.05. (ROX: Respiratory rate oxygenation index, mROX: modified Respiratory rate oxygenation index.)

Index / timepoint	Parameters	Cut-point	Sensitivity	Specificity
ROX index at baseline	Youden's J	4.59	0.643	0.692
	Eff. at P = 0.01	7.23	0.286	1
	Eff. at P = 0.05	7.23	0.286	1
mROX at baseline	Youden's J	4.1	0.571	0.846
	Eff. at P = 0.01	6.8	0.286	1
	Eff. at P = 0.05	6.8	0.286	1
ROX at six hours	Youden's J	4.47	0.643	0.769
	Eff. at P = 0.01	6.04	0.286	1
	Eff. at P = 0.05	6.04	0.286	1
mROX at six hours	Youden's J	3.34	0.857	0.769
	Eff. at P = 0.01	5.57	0.214	1
	Eff. at P = 0.05	5.57	0.214	1

The ROC curves and respective Youden’s J estimation curves for ROX and mROX at baseline and six hours are presented in Figs. 2 and 3, respectively. While the Youden’s J cut-off point value for mROX at baseline (i.e., 4.1) had the highest specificity of 84.6%, the Youden’s J cut-off point value for mROX at six hours (i.e., 3.34) had the highest sensitivity of 85.7%, and sensitivity plus specificity of 162.6%.

Discussion

In the present observational pilot study, the mROX showed slightly better but statistically insignificant predictive accuracy for HFNC failure than the ROX index of respective time points. These findings are in line with Roca O et al.’s analysis, where they also found that the diagnostic accuracies of ROX index with SpO_2/FiO_2 and PaO_2/FiO_2 (mROX index) were statistically indifferent at two, six, and 12-hours [12]. Unfortunately, the efficacy of both ROX and mROX was only fair to good, and none of the indexes at baseline or six-hour could achieve a sensitivity and specificity even near 90%. The maximum sensitivity was achieved by mROX at six hours (i.e., 87.55%) at a cut-off value of 4.05, but the specificity was only 63%. While a screening tool does not require high specificity, high sensitivity is desirable to detect most true positive cases. In that context, ROX at six hours and mROX at baseline and six hours appear to have the potential as they all have a sensitivity of > 70%. Nonetheless, for a screening test to be clinically helpful, both sensitivity and specificity are essential, and a criterion based on sensitivity + specificity of

1.5 and above is considered [13]. The only screening test that qualified our pilot cohort's criteria was mROX at six hours. The sensitivity and specificity of the ROX index in our study were similar to the other contemporary studies and meta-analyses [14, 15].

The present study hypothesis was based on the clinicopathological features of COVID-19 pneumonia and ARDS. As respiratory rate and oxygenation are altered in COVID-19 AHRF patients compared to non-COVID-19 AHRF patients, we assumed that the ROX and mROX index may have altered efficacy in predicting HFNC O_2 therapy in COVID-19 patients. The failure to find mROX significantly better as a predictor might be explained by the need for FiO2 during HFNC therapy. These patients are mostly moderate-to-severely ill and usually do not require 100% FiO_2. At the relatively lower FiO2, SpO_2/FiO_2, and PaO_2/FiO_2 correlate well even in COVID-19 patients [16]. As the need for FiO2 increases toward 100% in patients receiving HFNC O_2 therapy, the chances of HFNC O_2 therapy failure also increase.

In their landmark study, Roca O et al. [4] reported ROX index at 12 hours as having the best prediction accuracy (area under ROC 0.74 [95% confidence interval, 0.64–0.84]) with the best cut-off point for ROX index estimated to be 4.88. Vega et al. [17] validated the utility of the ROX index as a predictor of HFNC failure for COVID-19 patients and reported almost similar results to Roca et al. The 12-hour ROX index was found to be the best predictor of intubation with an AUC of 0.7916 [CI 95% 0.6905–0.8927] and the best threshold was 5.99 [Specificity 96% Sensitivity 62%]. Even the multivariate analysis to determine the predictive factors for HFNC failure by Lun CT et al. [18] found ROX index at 12has one of the significant entities. However, the time-point for best prediction is not similar. Ferrer et al. [19] found the ROX index as a good predictor in their observational study. They reported ROX index at 24has the best predictor of success (AUC 0.826, 95%CI 0.593-1.00) with a cut-off point of 5.35 (Sensitivity 0.91, Specificity 0.79, PPV 0.92, NPP 0.79). On the other hand, Suliman LA et al. [20], enrolling COVID-19 patients, found that ROX on day-1 was a significant predictor of intubation through regression analysis.

In their systematic review and meta-analysis, Prakash et al. [21] assessed the ROX index as a predictor of HFNC failure in COVID-19 patients with AHRF; eight retrospective studies (n = 1301 patients) were considered for analysis. The meta-analysis yielded a summary area under the curve (sAUC) 0.81 (95% CI, 0.77–0.84) with sensitivity of 0.70 (95% CI, 0.59–0.80) and specificity of 0.79 (95% CI, 0.67–0.88) of ROX index for predicting HNFC failure. The positive and negative likelihood ratio was 3.0 (95% CI, 2.2–5.3) and 0.37 (95% CI, 0.28–0.50), respectively, and was strongly associated with good predictive accuracy (diagnostic odds ratio 9, 95% CI, 5–16). Similarly, the systematic review and meta-analysis by Zhou et al. [22] for ROX index as a predictor of HFNC outcome in pneumonia patients with AHRF found good predictive performance for successful HFNC weaning in patients with an area under ROC of 0.81 (95% CI 0.77–0.84), a pooled sensitivity and specificity of 0.71 (95% CI 0.64–0.78), and0.78 (95% CI 0.70–0.84) respectively. The analyses also suggested that the ROX index was a reliable predictor of HFNC success in patients with COVID-19 pneumonia. The area under the curve analysis of our cohort for both ROX and mROX index at admission and six hours were also in the same line of these studies.

Although most of the study using ROX has stressed the HFNC failure, Suliman LA et al. [20] studied the ROX and mROX for predicting intubation of COVID-19 patients. At the time of intubation, the ROX and mROX median (min-max) values were 3.88 (3.33–6.09) and 5 (3.14–5.52), respectively. In contrast to Suliman LA et al.'s [20] study, 11 out of 13 failure patients were initially tried on Bilevel pressure support non-invasive ventilation before intubation and invasive mechanical ventilation. Nevertheless, the entire but one patient ultimately required IVM. The mROX and ROX values at six hours and 12 hours in our failure cohort were within the range of the study Suliman LA et al.'s [20] study, which required intubation, indicating the efficiency of the indexes for not only predicting HFNC failure but also predicting intubation. Rochwerg et al. [23] performed a systematic review and meta-analysis to evaluate the safety and efficacy of HFNC in patients with acute hypoxemic respiratory failure. Nine randomized controlled trials were included (n = 2093 patients) and analyzed. They reported that HFNC usage reduced the need for invasive mechanical ventilation compared to conventional oxygen therapy (RR 0.85[95% CI 0.74–0.99 with low certainty).

Further, the use of HFNC reduced the need for escalation of therapy, although it did not affect ICU and hospital length of stay. Notably, delaying intubation leads to increased mortality. In this context, using any of the ROX or mROX indexes to predict failure and intubation might be an excellent clinical practice despite not having excellent sensitivity and specificity and other limitations [24].

The other intriguing observational finding is the ROX or mROX values trend. Persistent lower values and decreasing trends over the 12 or 24h were the characteristics of the cohort who failed the HFNC. The findings also corroborate with the data presented by Suliman LA et al. [20], where the cohort requiring intubation also showed decreasing trend of the ROX value over the 72-hours.

However, our study is limited because it was an observational study conducted in a single center and a pilot study. The decision to convert artificial respiratory support from HFNC to NIV (BiPAP) or IMV was at the treating physician's discretion, and no written or strict protocol was followed. We intended to identify the better screener at the earliest and therefore stressed primarily within six-hour of the HFNC application. Although the patients were followed until they were either discharged or in heavenly abode, limited data deterred us from analyzing at delayed time points. Sedation is another factor that impacts the tolerance and respiratory rate during any non-invasive artificial respiratory support. It bears importance in the context that the sedation requirements of COVID-19 patients are very high and variable [25]. We did not monitor the sedation levels and drugs used for the same, which might have a minor impact on our results.

Conclusion

Both ROX and mROX at baseline and six hours had fair-to-good sensitivity, specificity, positive and negative predictive values, and area under the ROC; the differences were statistically insignificant. The accuracies of the indices were better at six hours than the baseline. Although both the indices can be used, only mROX at six hours with a mean value of 4.05 and a cut-off value of 3.34 had a sensitivity plus

specificity at 1.56 and 1.63 (i.e., 156% and 163%), respectively be considered a clinically valuable screener. A falling trend or failure to improve the index values over time and progressively increasing need for FiO2 is a vital observation to predict progression towards HFNC oxygenation failure.

Declarations

Conflicts of interests: The authors declare no conflicts of interests

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References

1. World Health Organization.: Rolling updates on coronavirus disease (COVID-19). Geneva; WHO: 31 Jul 2020. (last accessed 10 May 2022). Available from URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
2. Agarwal A, Basmaji J, Muttalib F, et al.: High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anaesth. 2020;1–32. doi: 10.1007/s12630-020-01740-2.
3. Alhazzani W, Møller MH, Arabi YM, et al.: Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46:854–87. doi:10.1007/s00134-020-06022-5
4. Roca O, Messika J, Caralt B, et al.: Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care. 2016;35:200–5. doi: 10.1016/j.jcrc.2016.05.022.
5. Roca O, Caralt B, Messika J, et al.: An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019;199:1368–76. doi: 10.1164/rccm.201803-0589OC.
6. Tobin MJ, Laghi F, Jubran A.: Why COVID-19 Silent Hypoxemia is Baffling to Physicians. Am J Respir Crit Care Med. 2020;202:356–60. doi:10.1164/rccm.202006-2157CP. doi:10.1164/rccm.202006-2157CP
7. Catoire P, Tellier E, de la Rivière C, et al.: Assessment of the SpO_2/FiO_2 ratio as a tool for hypoxemia screening in the emergency department. Am J Emerg Med. 2021;44:116–120. doi: 10.1016/j.ajem.2021.01.092.
8. Brown SM, Grissom CK, Moss M, et al.: Nonlinear Imputation of Pao2/Fio2 From Spo2/Fio2 Among Patients With Acute Respiratory Distress Syndrome. Chest 2016;150:307–13. doi:

10.1016/j.chest.2016.01.003.

9. Madan A.: Correlation between the levels of SpO2and PaO2. Lung India 2017;34:307–8. doi: 10.4103/lungindia.lungindia_106_17.
10. Karim HM, Esquinas AM.: Success or Failure of High-Flow Nasal Oxygen Therapy: The ROX Index Is Good, but a Modified ROX Index May Be Better. Am J Respir Crit Care Med. 2019;200:116–7.
11. Viechtbauer W, Smits L, Kotz D, et al.: A simple formula for the calculation of sample size in pilot studies. J Clin Epidemiol. 2015;68:1375–9. doi: 10.1016/j.jclinepi.2015.04.014.
12. Roca O, Caralt B, Ricard JD.: Reply to Tatkov, to Karim and Esquinas, and to Tulaimat. Am J Respir Crit Care Med. 2019;200:117–9. doi: 10.1164/rccm.201903-0571LE.
13. Power M, Fell G, Wright M.: Principles for high-quality, high-value testing. Evid Based Med. 2013;18:5–10. doi: 10.1136/Feb-2012-100645.
14. Junhai Z, Jing Y, Beibei C, et al.: The value of ROX index in predicting the outcome of high flow nasal cannula: a systematic review and meta-analysis. Respir Res. 2022;23:33. doi: 10.1186/s12931-022-01951-9.
15. Myers LC, Mark D, Ley B, et al.: Validation of Respiratory Rate-Oxygenation Index in Patients With COVID-19-Related Respiratory Failure. Crit Care Med. 2022. (online ahead of print) doi: 10.1097/CCM.0000000000005474.
16. Kumar A, Aggarwal R, Khanna P, et al.: Correlation of the SpO2/FiO2 (S/F) ratio and the PaO2/FiO2 (P/F) ratio in patients with COVID-19 pneumonia. Med Intensiva. 2021. (online ahead of print). doi: 10.1016/j.medin.2021.10.005.
17. Vega ML, Dongilli R, Olaizola G, et al.: COVID-19 pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU. Authors' reply. Pulmonology. 2021;27:475–476. doi: 10.1016/j.pulmoe.2021.07.001.
18. Lun CT, Leung CK, Shum HP, et al.: Predictive factors for high-flow nasal cannula failure in acute hypoxemic respiratory failure in an intensive care unit. Lung India. 2022;39:5–11. doi: 10.4103/lungindia.lungindia_122_21.
19. Ferrer S, Sancho J, Bocigas I, et al.: ROX index as predictor of high flow nasal cannula therapy success in acute respiratory failure due to SARS-CoV-2. Respir Med. 2021;189:106638. doi: 10.1016/j.rmed.2021.106638.
20. Suliman LA, Abdelgawad TT, Farrag NS, et al.: Validity of ROX index in prediction of risk of intubation in patients with COVID-19 pneumonia. Adv Respir Med. 2021;89:1–7. doi: 10.5603/ARM.a2020.0176.
21. Prakash J, Bhattacharya PK, Yadav AK, et al.: ROX index as a good predictor of high flow nasal cannula failure in COVID-19 patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. J Crit Care. 2021;66:102–108. doi: 10.1016/j.jcrc.2021.08.012.
22. Zhou X, Liu J, Pan J, et al.: The ROX index as a predictor of high-flow nasal cannula outcome in pneumonia patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. BMC Pulm Med. 2022;22:121. doi: 10.1186/s12890-022-01914-2.

23. Rochwerg B, Granton D, Wang DX, et al.: High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019;45:563–72. doi: 10.1007/s00134-019-05590-5.
24. Gallardo A, Zamarrón-López E, Deloya-Tomas E, et al.: Advantages and limitations of the ROX index. Pulmonology. 2022:S2531-0437(22)00071-X. doi: 10.1016/j.pulmoe.2022.02.008.
25. Nayak P, Karim HMR.: Requirement and response pattern for sedatives in COVID-19 patients requiring non–invasive ventilation: A pilot observation. Anaesth. Pain Intensive Care 2022;26:260–262; **doi**: 10.35975/apic.v26i2.1809

Figures

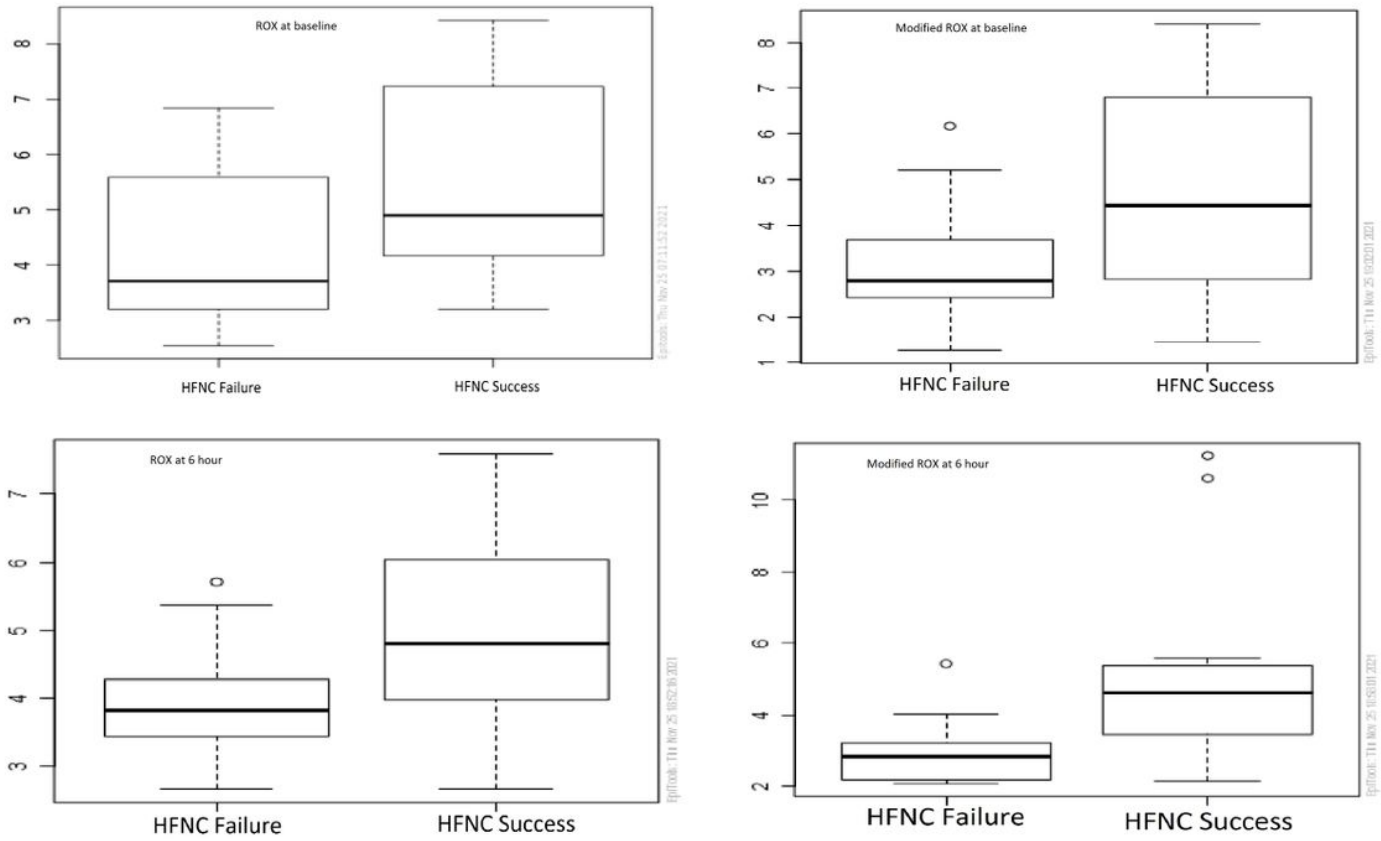

Figure 1

Box and plot representation of ROX and mROX at the baseline and six hours. (ROX: Respiratory rate oxygenation index, mROX: modified Respiratory rate oxygenation index.)

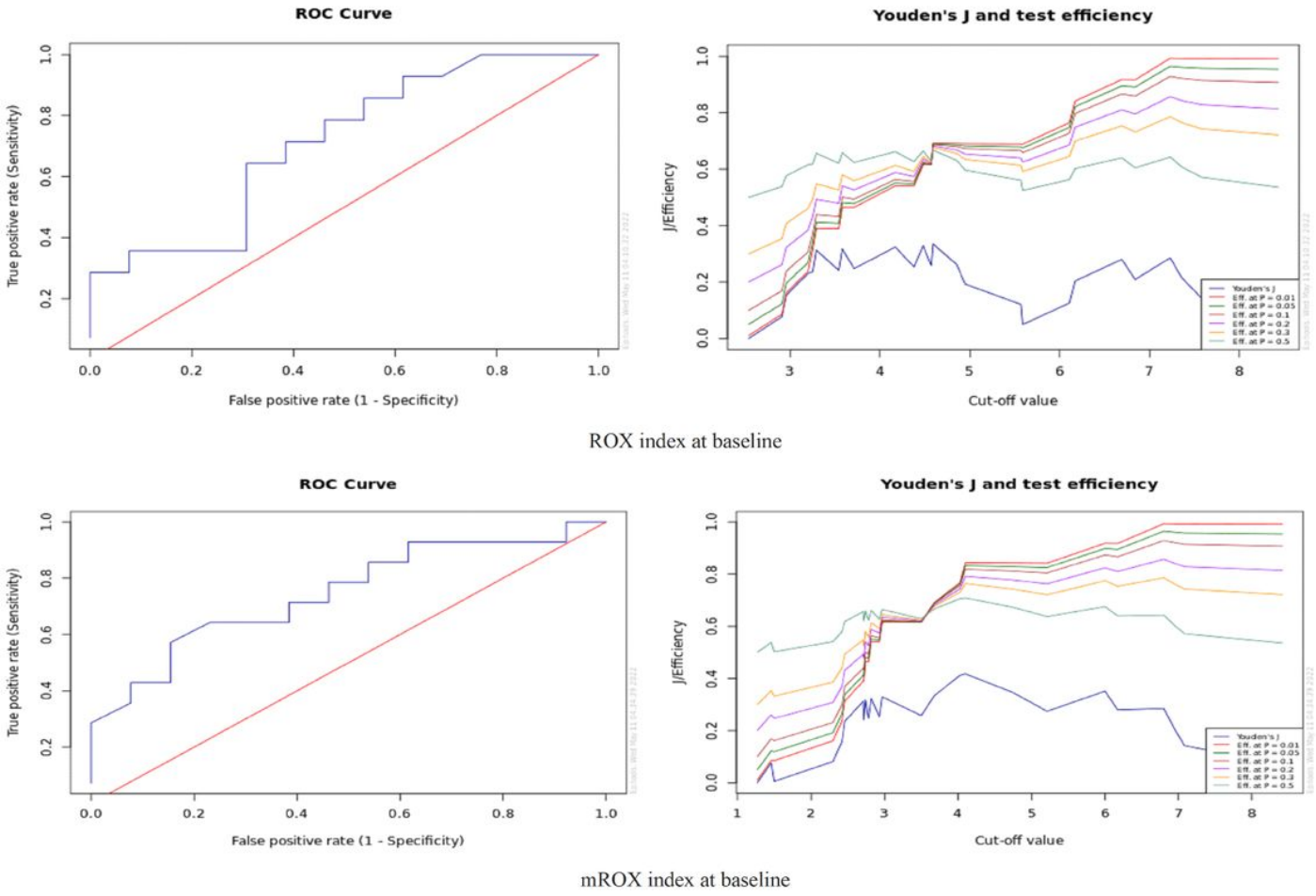

Figure 2

ROC curves and respective Youden's J estimation curves for ROX and mROX at baseline. (ROC: Receiver operating characteristic, ROX: Respiratory rate oxygenation index, mROX: modified Respiratory rate oxygenation index.)

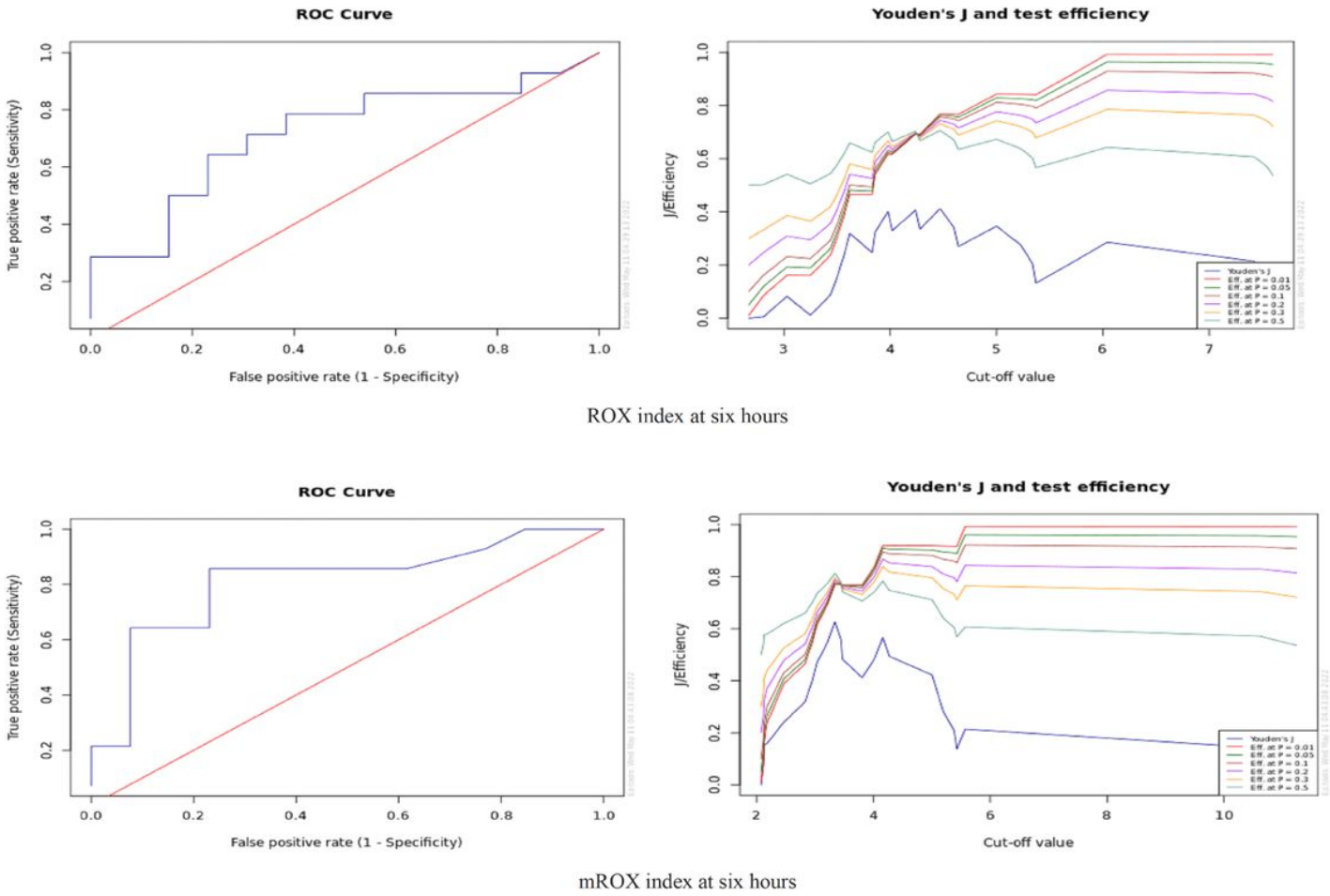

Figure 3

ROC curves and respective Youden's J estimation curves for ROX and mROX at six hours. (ROC: Receiver operating characteristic, ROX: Respiratory rate oxygenation index, mROX: modified Respiratory rate oxygenation index.)