The role of ROX and mROX indices in predicting intubation in COVİD 19 patients treated with high flow nasal oxygen in Intensive Care Unit

İlkay Ceylan, Halil Erkan Sayan, Korgün Ökmen, Umut Öylevi

Anesthesiology and Reanimation Department, TC University of Health Sciences, Bursa Training and Research Hospital, Bursa, Turkey

Corresponding author:
İlkay Ceylan.
E-mail: ceylanilkay@yahoo.com;
ORCID: 0000-0003-3306-3107

Abstract

Aim: In Coronavirus disease 2019 (COVID-19) - related respiratory failure, high-flow nasal oxygen (HFNO) therapy may delay invasive ventilation. The respiratory rate oxygenation (ROX) and modified ROX (mROX) indices, which can predict the need for invasive ventilation, can also be used in patients with COVID-19 with respiratory failure. The aim of the study was to verify the effectiveness of ROX and mROX to predict entubation need in HFNO therapy patients in intensive care unit.

Material and methods: This retrospective study included 41 patients in the final evaluation.

Results: The overall mortality of patients with similar demographic and laboratory data was 60,97%. Invasive ventilation was required in 27 patients. The cutoff values for prediction of intubation for ROX and mROX at 6 h were determined as 4,95 and 6,01. Conclusion: These indices can predict the need for invasive ventilation during the follow-up of COVID 19 patients who undergo HFNO and can help prevent adverse outcomes.

Key words: ROX, mROX, HFNO, COVİD19, ICU

Introduction

High-flow nasal oxygen (HFNO), a humidified and heated oxygen-rich gas, is administered in patients by special nasal high-flow cannulas. Generally, high flow rates of 30–60 L/min are used. The high flow provides a more stable inspiratory oxygen concentration and positive end-expiratory pressure in the airways compared with conventional oxygen therapy [1]. HFNO has been found to reduce the work of breathing and need for invasive ventilation by reducing physiological dead space in studies involving patients with respiratory failure due to other viral pneumonias [1].

The initial message from the Chinese medical teams was to intubate Coronavirus disease 2019 (COVID-19) patients early, somewhere around a 5-6 liter by nasal prong O2 requirement. However, this also has come at a cost. Mechanical ventilation is inherently associated with a number of well described and accepted complications [2]. Also the use of HFNO was limited in the early stages of the COVID-19 pandemic due to fear of the increased risk of viral transmission through aerosol in patients who developed respiratory failure [3]. The use of HFNO has increased in this patient group, with increasing data indicating that aerosol transmission is not as efficient

a transmission route as it was speculated initially [4]. However to the best of our knowledge there is no evidence at an advanced level regarding the use of HFNO in acute respiratory failure due to COVID-19 pneumonia. Despite HFNO large swings in intra-pleural pressure may result in self-inflicted lung injury and worsen the disease process. For this reason it has been stated that delayed intubation and mechanical ventilation support in patients with COVID-19 undergoing HFNO may increase the mortality rate [5].

Respiratory rate oxygenation (ROX) index was developed by Roca et al. to predict the need for intubation and mechanical ventilation in patients who underwent HFNO due to acute respiratory failure secondary to bacterial pneumonia [6]. ROX index, which is defined as ratio of SpO2/FiO2 to the respiratory rate, is easily measured at the bedside, and an ROX score of <3.47 at 6 h has been considered a predictor of HFNO failure. In addition, Goh et al. created a modified ROX (mROX) index incorporating heart rate to improve its diagnostic value [7]. However, data are limited with the use of these two indices in acute respiratory failure due to COVID-19 in intensive care [8].

Our purpose was to evaluate the ROX [6] and

mROX [7] index defined as an early marker of HFNO response and a potential predictor of its failure in the COVİD19 ICU patients with intended to contribute to literature.

Material and methods

The study was planned as a single-center retrospective study. The study was initiated after obtaining an approval from the The study was initiated after obtainig an approval from the ethical commitee. (2011-KAEK-25 2020/06-05 TC SBÜ Bursa Yüksek İhtisas EAH KAEK) ethics committee of YYYY university/institute. Nasopharyngeal swab polymerase chain reaction (PCR) positive patients with COVID-19 with respiratory failure with respiratory rate >30/min and SpO2 <90% despite receiving oxygen with a reservoir mask at 15 L/min and treated with HFNO as first-line ventilator support/who received only HFNO during intensive care follow-up in May and June in the 21-bed adult general intensive care unit of our hospital were included in the study. Patients who underwent noninvasive mechanical ventilation at baseline and did not receive HFNO therapy were excluded from the study. HFNO-related data was collected from admission until HFNO weaning or intubation which defined HFNO failure.

Medical therapy

COVID-19 treatments were arranged according to the current treatment guidelines based on national treatment protocols [9]. 6 mg dexamethasone or 1 mg/kg methylprednisolone treatment, defined as additional treatment in these protocols, was administered to all patients.

HFNO therapy

HFNO therapy was administered via Draeger (Lübeck, Germany) Evita V300 mechanical ventilator. HFNO therapy starts with 50 L/min flow, FiO2 1 and 37°C air temperature. The target SpO2 was set at 90%. When SpO2 was ≥ 90%, the oxygen ratio was first reduced to 0.6, and if no regression was detected in the follow-up values, the flow rate was reduced. HFNO therapy was discontinued in patients with oxygen rate of 0.5 and flow rate of 20 L/min. During HFNO therapy, a surgical mask was placed on the patient's face to reduce aerosol emission, and intermittent prone positioning was applied as per the protocol. Patients with worsening of oxygen saturation levels or clinical deterioration despite HFNO therapy were detected to require intubation and switched to invasive/noninvasive mechanical ventilation.

Outcome measures

ROX and mROX indices at 2, 6, 12, and 24 h following HFNO were determined as the primary outcome measures. ROX index was calculated by dividing the SpO2/Fio2 value by the number of respiration and mROX by dividing the ROX value by the heart rate and multiplying with 100. The duration of HFNO, time until intubation or HFNO withdrawal (days) and hospitalization laboratory parameters were recorded as secondary outcomes. The demographic data of the patients were taken from the electronic database of our hospital.

Statistical analysis

Statistical analyses were performed using SPSS 22 (IBM, USA) package program with significance of $p < 0.05$. Categorical variables are described as number (%) and numerical variables as median and interquartile range (IQR). Categorical variables were evaluated using the appropriate chi-square and Fisher's exact test. Mann–Whitney U test was used to determine the statistical difference between the numerical values of the ROX and mROX at 2, 6, 12, 18, and 24-h and the successful and failed HFNO groups. The effect of statistically significant parameters on survival was examined using COX regression analysis. Receiver operating characteristic (ROC) curve analysis of the values determined to have an effect on survival was performed, and the cutoff values and area under the curve values for ROX and mROX were calculated.

Results

During the study period, 127 patients were admitted to the intensive care unit. In total, 41 patients, 23 males and 18 females, meeting the study criteria were included in the evaluation (Table 1). Of the patients, 33 were found to have at least one additional disease. There was no statistically significant difference between the groups in terms of comorbidities. The most common additional disease was diabetes mellitus (48,78%). No statistically significant difference was found between the d-dimer, ferritin, fibrinogen, c reactive protein, values of the patients. Among them, 27 required intubation and 16 were discharged from the intensive care unit (Table 2). In total, 25 (60.97%) of patients died in the intensive care unit.

ROX and mROX indices diagnostic efficacy

COX analysis was performed to predict the need for intubation and evaluate its effect on survival in our study patients. In the survival analysis performed for statistically significant scores of mROX at 6, 18, and 24 h and ROX at 6 h (Table 2), it was determined that the 6-h mROX and ROX values had a statistically significant negative effect on survival (mROX: $p = 0.02$, hazard ratio [HR] = 0.77 [0.62–0.96]; ROX: $p = 0.04$, HR = 0.72 [0.53–0.98]).

		Table 1		Demographic Data

	HFNO succeed (n:14)	HFNO failed (n:27)	z	p
Age	72.00 (59.50-78.75)	70.00 (65.00-79.00)	-0.51	0.61
APACHE1 2	19.50 (15.00-22.50)	21.00 (16.00-25.00)	-1.07	0.29
ICU LOS2 (day)	10.50 (8.75-14.25)	9.00 (6.00-13.00)	-1.09	0.28
HFNO3 Therapy (day)	6.00 (4.75-9.25)	3.00 (2.00-4.00)	-3.34	0.01
Gender n, (%)				
Male	8 (34.8)	15 (65.2)	X2:0.03	0.92
Female	6 (33.3)	12 (66.7)		

1:Acute Physiologic and Chronic Health Evaluation Score 2, 2:Intensive Care Length of Stay, 3: High Flow Nasal Oxygen
z: Mann Whitney-U test; X2: Chi-square test

|		Median (IQR 1-3)	z	p
ROX 2	HFNO succeeded	4.38 (3.33-6.57)	-0.811	0.417
	HFNO failed	4.80 (4.31-6.14)		
ROX 6	HFNO succeeded	4.61 (3.95-5.83)	-2.145	0.032
	HFNO failed	5.65 (4.69-6.94)		
ROX 12	HFNO succeeded	4.94 (3.83-6.28)	-0.564	0.573
	HFNO failed	5.21 (4.63-6.19)		
ROX 18	HFNO succeeded	4.62 (4.10-6.23)	-1.457	0.145
	HFNO failed	5.97 (4.74-7.35)		
ROX 24	HFNO succeeded	4.08 (3.73-5.11)	-1.54	0.124
	HFNO failed	4.92 (4.14-6.33)		
mROX2	HFNO succeeded	6.31 (4.76-7.91)	-1.70	0.09
	HFNO failed	5.19 (3.58-6.87)		
mROX6	HFNO succeeded	7.50 (6.14-10.17)	-3.24	0.01
	HFNO failed	5.00 (4.24-6.50)		
mROX12	HFNO succeeded	7.42 (5.49-8.74)	-1.80	0.07
	HFNO failed	5.60 (3.93-7.49)		
mROX18	HFNO succeeded	7.75 (5.86-8.80)	-3.12	0.01
	HFNO failed	5.36 (4.14-6.35)		
mROX 24	HFNO succeeded	7.11 (5.41-7.87)	-2.83	0.01
	HFNO failed	4.65 (3.84-6.00)		

z: Mann Whitney-U test
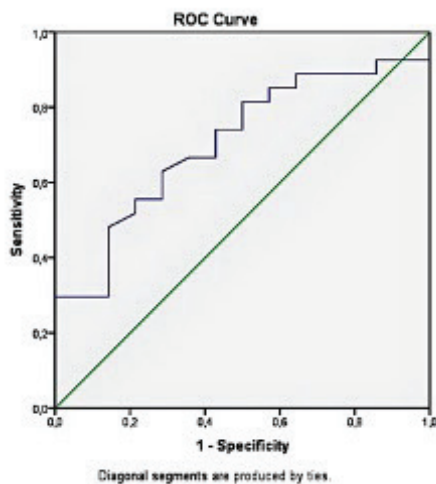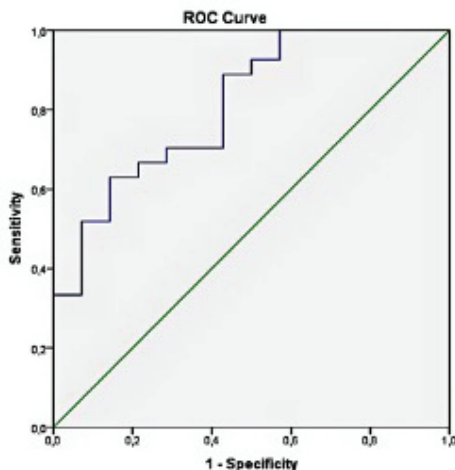

Figure 2 - ROX index ROC curve

Figure 2 - mROX index ROC curve

ROC analysis was performed to determine the cutoff values of the 6-h ROX and mROX values, which were statistically significant. From this analysis, the cutoff point for HFNO success was 6.01 for mROX (sensitivity 62.96%, specificity 85.71%, area under the curve 0.812 with $p<0.05$) and 4.95 for ROX (sensitivity 60.61%, specificity 71.43%, area under the curve 0.706 with $p<0.05$; Figures 1 and 2; area under ROC curves).

Discussion

In our intensive care unit, 14 (34.14%) of our 41 patients who underwent HFNO due to respiratory failure related to PCR-positive COVID-19 pneumonia did not require invasive mechanical ventilation. Of the patients, 27 were switched to invasive mechanical ventilation and 2 were able to wean off the invasive ventilation. In our patients who underwent HFNO, the 6-h ROX and mROX values were found to be significant in predicting the need for invasive mechanical ventilation, and patients with cutoff values <4.95 and <6.01 needed intubation.

Although there are limited data regarding the use of HFNO in respiratory failure due to COVID-19 pneumonia, there are studies indicating its potential reducing the need for invasive ventilation in patients with COVID-19 [3,10]. HFNO may help avoid the potential risks of endotracheal intubation and mechanical ventilation and compensate for the lack of mechanical ventilators in pandemic conditions. However, it is hard to determine when to switch to invasive ventilation in patients with COVID-19. Some authors have emphasized that in patients breathing spontaneously, deep sighing respiration will cause large fluctuations in transpulmonary pressure, resulting in self-induced lung injury [11]. Therefore, they recommended early intubation. However, the studies conducted were not sufficient to show difference in survival between early and late intubations in patients with COVID-19 [12,13]. As the intubation criteria and times differ in such studies, it is difficult to make a comparison. In our patients, intubation need was decided by the ICU physician and the patient's clinical parameters were prioritized. In the group unresponsive to HFNO among our patients, the mean time until intubation and invasive ventilation was 3 days, and it was relatively late. Likewise, the mortality rate (60.97%) of our patients who were unresponsive to HFNO and switched to invasive mechanical ventilation was found to be high. We believe that this high rate might be due to the pathophysiological differences of classic acute respiratory distress syndrome and respiratory failure due to COVID19 rather than the timing of intubation [14].

ROX index recommended by Roca et al. to predict the need for invasive ventilation in patients who developed respiratory failure due to pneumonia and underwent HFNO can also be used in patients with COVID-19 [15–17]. In our study, ROX and mROX indices were evaluated intermittently at the first 2, 6, 12, 18, and 24 h of HFNO application. We determined that the 6-h values of these indices could predict intubation in our patients. In addition, the cutoff values for 6-h ROX and mROX values to predict intubation in our study were 4.95 and 6.01, respectively. Roca et al. stated that patients with a 6-h ROX value >4.88 had lower need for intubation. Although this value has been evaluated in patients with non-COVID-19 respiratory failure, our results are also remarkably close to these values. Belz et al. used the original cutoff value of 4.88 to predict the need for intubation in intensive care patients who underwent HFNO due to COVID-19 and found 81% sensitivity and 38% specificity [18]. In our study, we determined that the cutoff value was 4.95 with 60.61% sensitivity and 71.43% specificity. According to our findings,

6-h ROX values can help predict patients who will benefit from HFNO. In addition, Suliman et al. monitored the ROX index for 3 consecutive days and evaluated their patients' intubation needs in the first week [15]. They stated that the ROX index (adjusted odds ratio [95% CI]: 16.9 [2.4–117], 0.77 [0.69–0.86]) measured only on day 1 was an independent factor in predicting intubation. Although we determined the need for intubation at any time as the endpoint for our study, intubation need emerged, on average, on day 3 in our patient group. This outcome, led us to think that the evaluated index could be used to predict the intubation need in a relatively short term. It seems reasonable to avoid unnecessary intubation and administer HFNO for a longer time by evaluating the ROX index in the patients.

Goh et al. in their studies on patients with non-COVID-19 respiratory failure stated that mROX was more effective in predicting the need for intubation for the same hours evaluated in patients who received HFNO compared with the original index of Roca et al [7]. In our study on patients with COVID-19, we found that 6-h mROX score <6.01 was effective in predicting the need for intubation. In addition, we found that 6-h mROX score was slightly more effective than the 6-h ROX index (sensitivity 62.96% and specificity 85.71%). We suggest that the index, which has not been validated yet but can be easily calculated at the bedside, can be used in addition to the original index to predict the need for invasive ventilation in patients with respiratory failure due to COVID-19 pneumonia who undergo HFNO. There is no study in the literature using mROX values in patients with COVID-19. The major limitation of this index, which is used in different disease groups, is that it is affected by drugs that affect heart rate.

The mROX index can be overestimated in the use of drugs such as beta blockers and opiates that may cause bradycardia. In patients using these drug groups, it may be necessary to evaluate the intermittent measurements and consider the trend of the mROX index instead of making a decision with a single measurement. Among our study patients, no one used drugs of these classes.

The 6-h mROX index evaluated within the scope of this study may be successful in predicting the success of HFNO therapy. We believe that following the standard medical (e.g., favipiravir and hydroxychloroquine) and additional (intermittent prone positioning) treatment protocols according to the national treatment protocol increases the accuracy of the results of the mROX index.

Limitation

The main limitation of this study is the retrospective design and small number of patients. Other limitations included the fact that although intubation criteria were specified, these criteria were flexed in some patients due to intubations performed under emergency conditions and busy schedule. Also we could not be able to add the percentage of lungs involvement with Murray score or any other equivalent which can help to better understand the HFNO failed patients. However, the standard treatment of COVID-19 pneumonia in our patients and the similar characteristics of the patient group might have weakened potential confounders.

Conclusion

HFNO might be effective as a first-line therapy in patients with COVID-19 in whom low-flow oxygen therapy is insufficient. Early administration may be effective to protect patients from the potential negative effects of intubation and mechanical ventilation. In addition uur study findings suggest that using indices such as ROX and mROX at the bedside may be important in monitoring the course of the disease and predicting the need for invasive ventilation.

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