Balkan Med J 2023;40:111-116

Rox Index Dynamics According to High Flow Nasal Cannula Success in Intensive Care Unit Patients with COVID-19-Related Acute Respiratory Failure

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Background: High-flow nasal cannula therapy has been shown to be useful in the treatment of patients with acute respiratory failure caused by severe acute respiratory syndrome-coronavirus disease-2. The ROX index can help predict the success of high-flow nasal cannula in coronavirus disease-19-related acute respiratory failure. However, the timing of ROX- index assessment is still unclear to protect the patients from complications due to early or delayed intubation.

Aims: To evaluate the relation between ROX index patterns within the first 48 hours of the therapy and high-flow nasal cannula success rates. The secondary aim was to determine other possible predictors of high-flow nasal cannula failure.

Study design: A cross-sectional study.

Methods: Patients admitted to the intensive care unit between April 2020 and January 2022 with coronavirus disease-19-related acute respiratory failure and treated with high-flow nasal cannula were included in the study. Patients' demographics, clinical characteristics and laboratory findings at intensive care unit admission; ROX indices at initiation, 2nd, 8th, 12th, 24th and 48th hours of high-flow nasal cannula; and outcomes were recorded.

Results: In the study period, 69th patients were managed with high-flow nasal cannula for at least 2 hours. While 24 patients (34.7%) were successfully weaned from high-flow nasal cannula, 45 (65.3%) patients failed. Overall mortality at day 28 was 44.9%. ROX indices were lower in the high-flow nasal cannula failure group through the 12th, 24th, and 48th hours of the therapy, no significant change was observed ($P = 0.33$). While an overall increase in ROX index patterns were detected in patients weaned from high-flow nasal cannula ($P = 0.002$). Pairwise analyses revealed that ROX indexes remain stable during the first 8th hours in both groups, then improved to 12th hours of the therapy in successfully high-flow nasal cannula-weaned patients.

Conclusion: Dynamic assessments of the ROX indexes could be more suggestive rather than a point assessment to identify patients who would benefit from the high-flow nasal cannula or deteriorate in coronavirus disease-19 related acute respiratory failure.

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 causes respiratory failure by severe lung involvement in about 19% of the patients[1] which is the leading cause of intensive care unit (ICU) admissions and mortality.[2-4] In the era of the pandemic, high-flow nasal cannula (HFNC) therapy's popularity has been raised due to shown success of the modality in de nova hypoxemic respiratory failure.[5-7]

HFNC has some physiological effects like reduction of inspiratory resistance[8] and work of breathing,[9] clearance of anatomical dead space in upper airways[10] and secretion mobilization[11] by providing oxygen-enriched, humidified gas mixture in high flows to the upper airway. These can reduce the need for invasive mechanical ventilation (IMV) and protect the patients from IMV-associated complications like pneumonia, ventilatory induced lung, and diaphragmatic injury. In studies involving patients admitted to the ICU for acute respiratory failure (ARF) with coronavirus

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Received: 13.06.2022 Accepted: 30.12.2022 Available Online Date: March 08, 2023 • DOI: 10.4274/balkanmedj.galenos.2022.2022-6-31

Available at www.balkanmedicaljournal.org

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Cite this article as:
Hancı P, Uysal A, Yüksel B, İnal V. Rox Index Dynamics According to High Flow Nasal Cannula Success in Intensive Care Unit Patients with COVID-19-Related Acute Respiratory Failure. *Balkan Med J.*; 2023; 40(2):111-6.

disease-19 (COVID-19), HFNC has succeeded in the range of 36-62%.[12-15]

However, the system cannot provide adequate positive pressure support for recruiting the closed alveolus in acute respiratory distress syndrome (ARDS). In addition, the inability to reduce transpulmonary pressure gradient swings may cause self-inflicted lung injury.[16] Moreover, delaying the intubation may raise further risks. Therefore, the estimation of which patient will benefit from the treatment and the duration of a successful treatment is important.[17]

The ROX index, defined as the ratio of oxygen saturation as measured by pulse oximetry/oxygen fraction (FiO_2) to respiratory rate and validated in patients with acute hypoxemic failure, can help predict the success of HFNC.[18] High predictive values of this index were also confirmed by several studies in COVID-19 related ARF.[19,20] However, the timing of ROX index assessment is unclear yet, and a dynamic assessment of the index could be more helpful to identify treatment success.

In this study, we investigated the efficacy of HFNC in patients admitted to the ICU because of COVID-19-related ARF. The primary aim of this study was to evaluate the relation between ROX index patterns within the first 48 hours of the therapy and HFNC success rates. The secondary aim was to determine other possible predictors of HFNC failure.

MATERIALS AND METHODS

This retrospective and cross-sectional study was conducted in Trakya University Hospital Respiratory Intensive Care Units which was approved by the Trakya University Clinical Research Ethics Committee (TÜTF-BAEK 2021/275) and the Turkish Ministry of Health (2021-06-07T10_06_44). Patients diagnosed with ARF due to lung involvement of laboratory-confirmed (RT-PCR) COVID-19 and managed with HFNC at ICU admission were included in the study between April 2020 and January 2022.

As per the Turkish Ministry of Health COVID-19 management guideline,[21] HFNC is indicated for patients with persistent hypoxemia or respiratory distress symptoms under low flow oxygen therapy systems. HFNC was administered in the ICU with HI-Flow Star™ (Dragerwerk AG & Co., Germany), which is set to deliver a flow rate up to 50 l/min with FiO_2 to keep the patient's SpO_2 above 90%.

If deterioration in the patient's level of consciousness, worsening dyspnea, malign arrhythmia, or hemodynamic instability were detected or more than 60% FiO_2 under 50 l/min flow rate was required to keep the patient's PaO_2/FiO_2 over 150 mmHg, it was considered a treatment failure. Non-invasive ventilation (NIV) or IMV was initiated as rescue therapy.

Data were abstracted from the hospital records and nurse charts. Patients' demographics, body mass indices, comorbidities, Charlson Comorbidity Indices,[22] disease severity scores [Acute Physiology and Chronic Health Assessment (APACHE),[23] Sequential Organ Failure Assessment (SOFA)[24]] and laboratory findings (hemogram, d-dimer, ferritin, C-reactive protein, procalcitonin, arterial blood gas parameters within 2 hours thereafter HFNC initiation) at ICU admission; ROX indices at initiation, 2nd, 8th, 12th, 24th and 48th hours of HFNC; and out-comes (ICU and hospital length of stay, in 28-day mortality) were recorded (Figure 2). ROX index was calculated using the formula (SpO_2/FiO_2)/respiratory rate.[18] Patients were excluded who were younger than 18 years old and HFNC failed within 2 hours of the therapy.

Statistical Analysis

Statistical analyses were performed using IBM SPSS software version 26.0 (IBM Corporation, Armonk, NY). Descriptive analyses were presented as count (percentage) for categorical variables or median [25th-75th percentile] for numerical variables. Baseline characteristics, ROX indices and outcomes were compared between patients weaned from HFNC or failed using chi-square analysis or Fisher's exact test, as appropriate for categorical variables and The Mann-Whitney U test for numerical variables. Friedman tests were conducted to test whether a significant change in ROX indices in the groups separately. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. A 5% type-I error level was used to infer statistical significance.

A post-hoc power analysis was conducted using G*Power3 (Faul, Erdfelder, Lang, & Buchner, 2007) to test the difference between two independent group means of ROX indices at 12th hour. Results indicated that effect size (d) was 0.72 and power was 0.86 at a significance criterion of α=0.05.

RESULTS

A total of 742 patients who were admitted to Trakya University Faculty of Medicine Hospital COVID-19 ICU between April 2020 and January 2022 were screened. Of these, 316 patients had laboratory-confirmed COVID-19 by RT-PCR. Two hundred forty-nine of them had respiratory failure with lung involvement of COVID-19 and 69 of them managed with HFNC for at least 2 hours and they were enrolled in the study (Figure 1).

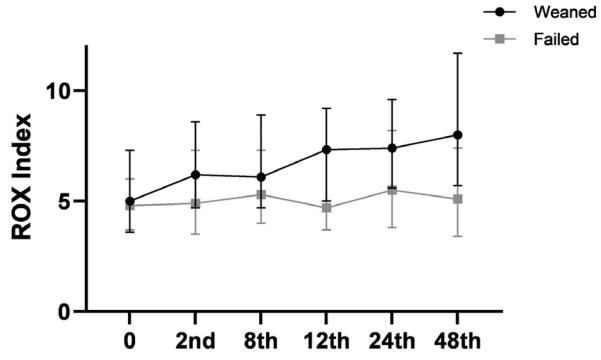

FIG. 2. Temporal Changes in ROX index at baseline, 2nd, 8th, 12th, 24th and 48th hours in groups weaned from HFNC and failed. Data points represent medians with 25-75 percentile, p values were assessed by Friedman test.

HFNC, high flow nasal cannula

Baseline characteristics and outcomes of patients are shown in Table 1. The median age of the patients was 63 [55-71]. Men were (62.3%) in the majority. Arterial hypertension was the leading comorbidity (52.2%) followed by diabetes mellitus (26.1). Eighteen (26.1%) patients had pre-existing chronic pulmonary disease. The Median Charlson comorbidity score was 4 [2-6]. Median PaO_2/FiO_2 ratio was 96.7 mmHg [79.1-135.2]. All the patients in the study met all the Berlin criteria (25) other than PEEP. The percent of patients with mild, moderate, and severe ARDS was 7.2 (n=5), 39.1 (n=27) and 53.6 (n=37) as per the Berlin definition,[25] respectively. HFNC was applied for a median duration of 48 hours [22.5-97.5]. Median ICU and hospital length of stay were 10 [7-14] and 17 [14-25] days, respectively. The 28-day mortality of the patients was 44.9%.

While 24 patients (34.7%) were weaned successfully from HFNC, 45 (65.3%) patients were failed; 40 of them intubated due to worsening or persistent respiratory distress (n=37) or hemodynamic instability (n=3), and the other 5 underwent NIV due to hypercapnia.

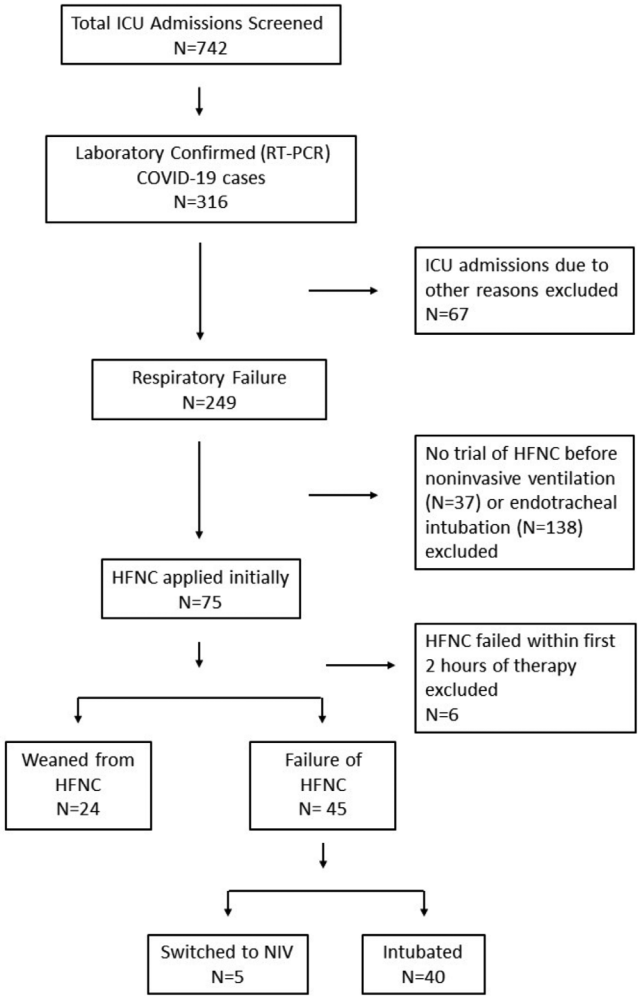

FIG. 1. The study flowchart shows screened, included and excluded, HFNC success/fail subjects' data.

ICU, intensive care unit; RT-PCR, reverse transcriptase-polymerase chain reaction; HFNC, high flow nasal cannula; NIV, non-invasive mechanical ventilation

Baseline characteristics and outcomes were compared among patients who failed or were weaned from HFNC (Table 1). Patients who weaned from HFNC (57.0 [45-66]) were younger than those who failed (64 [57-74]) (p = 0.01). Although there was no difference in comorbidities between the groups, Charlson comorbidity Index (p = 0.04) was higher in patients who failed (4 [2-6]) than in weaned ones (2 [1-5]). Groups were not different in terms of APACHE II (p = 0.18) and SOFA score (p = 0.68). Arterial blood gas parameters after initiation of HFNC were not different between groups.

Patients weaned from HFNC received this therapy for longer (85.5 [42.7-127.2] vs. 37 [16.5-67.5]) (p = 0.001) and ICU LOS was lower in this group (7 [5-10]) than the patients HFNC failed (12 [9-16]) (p < 0.001). The twenty-eight-day mortality rate was 68.9 % in patients who HFNC failed. Patients who HFNC succeed did not die within 28th day of ICU admission.

ROX indices at the initiation, 2nd, 8th, 12th, 24th and 48th hours of HFNC therapy were compared between patients who failed or successfully weaned from HFNC (Table 2). ROX indices were lower in the twelfth, 24th, and 48th hours of the therapy in the HFNC failed group than in the weaned group. Figure 1 shows the temporal changes in ROX indices of the two groups. There was an overall increase in the ROX index of patients weaned from HFNC (P = 0.002), while it did not change in HFNC-failed patients (p=0.33). Pairwise analyses revealed that the ROX index remain stable during the first 8th hours but increased and remained stable after 12th hours of the therapy in patients weaned from HFNC (Supplement Table 1).

DISCUSSION

In this study, 69 patients with COVID-19-related respiratory failure who received HFNC therapy in intensive care were evaluated. Forty-five (65.2%) patients switched to NIV or IMV due to HFNC failure. The overall mortality of patients was 44.9%. The ROX indices were similar for HFNC failed or succeeded patients during the first 8 hours of treatment. The improvement of the ROX index at the 12th hour was determined as a differentiation point for patients who would succeed or fail. After that, ROX indices progressively improved in the success group according to the failed group. Elderly, multiple comorbidities and lower platelet counts were related to HFNC failure.

HFNC therapy is an oxygen supplementation method known to reduce inspiratory effort and respiratory workload,[26] and improves clinical outcomes such as IMV need and mortality, as a result of many physiological contributions in acute hypoxemic respiratory failure.[5-7] The healthcare system has been challenged by the COVID-19 outbreak, with the sudden increase in the number of patients with severe respiratory failure that cannot be met by the number of intensive care beds and mechanical ventilators available. The use of non-invasive respiratory support systems is increased to prevent intubation and to allow weaning from invasive mechanical ventilation. Due to its better tolerance by patients and ease of

TABLE 1. Presentation and Comparisons of Basic Characteristics, Treatments and Outcomes of Subjects Treated with HFNC.

	All (n=69)	Weaned (n=24)	Failed (n=45)	*P*
Demographics				
Age, year	63 [55-71]	57.0 [45-66]	64 [57-74]	**0.01**
Male gender*	43 (62.3)	13 (54.2)	30 (66.2)	0.30
BMI, kg/m^2	29.3 [26.7-32]	29.6 [26.6-34.7]	29.0 [26.5-31.6]	0.47
Comorbidities*				
Any	58 (84.0)	19 (79.2)	39 (88.6)	0.30
Hypertension	36 (52.2)	11 (45.8)	25 (55.6)	0.44
Diabetes mellitus	18 (26.1)	4 (16.7)	14 (31.1)	0.19
Chronic pulmonary disease	18 (26.1)	5 (20.8)	13 (28.9)	0.46
Malignancy	15 (21.7)	4 (16.7)	11 (24.4)	0.45
Chronic kidney disease	10 (14.5)	5 (20.8)	5 (11.1)	0.30
Chronic heart disease	10 (14.5)	2 (8.4)	8 (17.8)	
Hematologic disease	5 (7.2)	1 (4.2)	4 (8.9)	0.42
Chronic liver disease	2 (2.9)	0 (0)	2 (4.4)	0.42
Rheumatological disease	1 (1.4)	0 (0)	1 (2.2)	0.65
Scores				
Charlson score	4 [2-6]	2 [1-5]	4 [2-6]	**0.04**
APACHE	13.0 [10.0-17.0]	13.0 [8.0-16.7)	14.0 [11.0-17.0]	0.18
SOFA	4 [3.0-6.0]	4 [3.0-6.0]	4 [4.0-5.0]	0.68
Laboratory findings				
Hemoglobin, g/dl	11.9 [10.6-13.6]	11.5 [10.6-13.4]	12.1 [10.6-13.6]	0.63
Neutrophil, 10^6/l	7.5 [4.7-11.3]	6.5 [4.0-10.6]	8.1 [5.2-11.9]	0.15
Lymphocyte, 10^3/l	500 [300-800]	450 [300-975]	500 [300-800]	0.79
Platelets, 10^6/l	213 [164-270]	257 [180-288]	196 [145-259]	**0.02**
D-dimer, mg/l	1.1 [0.69-2.39]	1.0 [0.66-1.81]	1.21 [0.72-3.67]	0.31
Ferritin, ng/ml	521 [289-1273]	569 [210-1002]	497 [312-1488]	0.52
C-reactive protein, mg/l	10.2 [5.1-15.8]	7.4 [3.9-10.7]	10.9 [5.4-175]	
Procalcitonin, ng/ml	0.16 [0.10-0.26]	0.17 [0.09-0.55]	0.15 [0.09-0.23]	0.81
pH	7.46 [7.41-7.48]	7.46 [7.42-7.50]	7.45 [7.41-7.47]	0.21
$PaCO_2$, mmHg	34.3 [30.2-38.1]	32.9 [30.0-39.0]	34.4 [30.5-39.0]	0.42
PaO_2, mmHg	66.1 [59.5-81.9]	73.5 [60.0-83.8]	65.5 [58.5-79.6]	0.42
FiO_2		67.5 [56.2-75]	70 [63-85]	0.10
PaO_2/FiO_2	96.7 [79.1-135.2]	102.5 [82.8-151.2]	93.5 [75.6-123.5]	0.09
ARDS severity				0.24
Mild	5 (72)	3 [12.5]	2 [4.4]	
Moderate	27 (39.1)	11 [45.8]	16 [35.6]	
Sever	37 (53.6)	10 [41.7]	27 [60]	
Outcome				
HFNC duration, hour	48 [22.5-97.5]	85.5 [42.7-127.2]	37 [16.5-67.5]	**0.001**
ICU-LOS, day	10 [7-14]	7 [5-10]	12 [9-16]	**<0.001**
Hospital- LOS, day	17 [14-25]	17 [13-23]	19 [14-25]	0.41
28-day mortality*	31 (44.9)	0 (0)	31 (68.9)	**<0.001**

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, oxygen saturation; FiO_2, fractional concentration of oxygen in inspired air; ARDS, Acute respiratory distress syndrome; HFNC, High flow oxygen cannula; ICU, intensive care unit; LOS, length of stay; *, n (%) Data expressed in median [interquartile range], and n (%).

TABLE 2. Presentation of ROX Indices at the Initiation, 2nd, 8th, 12th, 24th and 48th Hours and Statistical Comparisons Between HFNC Weaned and Failed Patients.

	Patients, n	All	Weaned	Failed	p
ROX index					
Initiation of HFNC	69	4.8 [3.6-6.8]	5 [3.6-7.3]	4.8 [3.7-6.0]	0.43
2nd hour of HFNC	69	5.5 [3.9-8.1]	6.2 [4.7-8.6]	4.9 [3.5-7.3]	0.11
8th hour of HFNC	67	5.4 [4.2-7.6]	6.1 [4.7-8.9]	5.3 [4.0-7.3]	0.14
12th hour of HFNC	64	5.5 [4.2-8.5]	7.34 [5.0-9.2]	4.7 [3.7-7.3]	**0.004**
24th hour of HFNC	52	6.4 [4.5-8.9]	7.4 [5.6-9.6]	5.5 [3.8-8.2]	**0.02**
48th hour of HFNC	37	6.0 [4.3-8.6]	8.0 [5.7-11.7]	5.1 [3.4-7.4]	**0.008**

HFNC, High flow nasal cannula

prone positioning under treatment,[27] HFNC has come to the fore, although the optimal noninvasive respiratory support method in acute hypoxemic respiratory failure and ARDS remains unclear.[28]

Many studies have examined the effectiveness of HFNC treatment in patients admitted to the ICU with COVID-19-induced acute hypoxemic respiratory failure. In these studies, HFNC failure was reported as 38-64% and mortality rates were 15-48% possibly due to the patients' PO_2/FiO_2 ratios being heterogeneous.[12-15] The higher HFNC failure (65.2 %) and mortality rates (44.9%) found in this study could be due to the severity of hypoxemia (PaO_2/FiO_2: 96.7 mmHg), compared to reported mean PO_2/FiO_2 (121-126 mmHg) in previous studies.[12,15]

In the Demoule et al.'[12] HFNC study, patients have similar characteristics to our study in terms of age, gender, comorbidity, SOFA score on the 1st day of ICU admission, and also pre-treatment PaO_2/FiO_2 ratio. They reported that 8% of patients were needed NIV and 56% received IMV on the 28th day of follow-up.[12] In another study conducted on patients with a very low PaO_2/FiO_2 ratio [68 (54-92) mmHg], mortality was found to be 92% in patients who HFNC failed.[13] HFNC success rates depended on patients' oxygenation status[29]. On the other hand, in our study the PaO_2/FiO_2 ratios were not deterministic for HFNC success. The smaller sample size we had possibly biased statistical power, the larger sample size could provide a more reliable comparison.

Delaying intubation or preventing SILI can be achieved by early predicting the success of NIV support therapies in patients with acute respiratory failure.[30] The ROX index has been assessed as a predictor of the need for intubation in patients supported with HFNC. In a study conducted by Roca et al.,[18] in patients who underwent HFNC for pneumonia and respiratory failure, a ROX index of 4.88 and above at the 2nd, 6th, or 12th hours of treatment was associated with a decrease in the need for IMV. The ROX index was also found to be reliable in COVID-19-related acute respiratory failure.[19,20] However, ROX index cut off values (2.7-5.99) vary due to differences in clinical practice, the timing of measurement, and patient population heterogeneity in available studies.[13,19,31-33] In a meta-analysis including 8 studies and 1301 patients with COVID-19 related acute respiratory failure, a ROX index cut off value of 5 and above showed the higher discriminative accuracy for the higher success rates. On the other hand, subgroup analyses showed that no significant discriminative difference was detectable through the first 6 hours of treatment.[20] In our study, ROC analysis was not included in the analyses due to threshold precisions that would have been poor with our small sample size.

In a multicenter, observational, retrospective study conducted by Chandel et al., it was determined that the diagnostic accuracy of the ROX index was highest at the 12th-hour measurements, and the reliability increased as the treatment time extended in these patients.[31] In a narrative review by Richard et al., an algorithm with ROX index was created to decide intubation at the 2nd, 6th, and 12th hours of the treatment in patients with ARF and the importance of dynamic follow-up was emphasized.[34] In another study evaluating HFNC success rates in relation to ROX index variability in the first 24 hours of treatment, showed that the ROX index tends to increase from the 1st hour of treatment in the success group.[35] In the study conducted by Vega et al. in COVID-19 patients, ROX indexes were checked at the 2nd, 6th, 12th, and 24th hours on the first day of treatment. The highest diagnostic accuracy of the ROX index was found at the 12th hour.[33] In our study, in accordance with the literature, the ROX index tended to increase from the 12th hour of the treatment in patients who HFNC succeeded. There was no significant increase in patients who failed. Significant differences were observed between the two groups at the 12th hour and later on.

In the ICU clinical practice, time-scaled ROX index calculations and a dynamic follow-up would be feasible. In order not to delay the mechanical ventilation decision, it would be advisable to be aware of the ROX index changes within hours, especially when the index is within the range of failure and success cut off values.

This study has many limitations. First, this study was conducted in a single centre with a small group of patients, retrospectively and observationally. Secondly, The ROX index was not used to determine the patients' HFNC failure decision. Since the sample size was not wide enough, ROC analysis hadn't been done to identify the ROX index cutoff value for predicting HFNC failure.

Thirdly, further analyses for factors determining HFNC failure could not be done due to the small sample size and non-homogeneous distribution.

Consequently, HFNC therapy success is linked to an increase in the ROX index in the first 48 hours of treatment in patients admitted to the critical care unit due to severe COVID-19-related respiratory failure. The improvement of the ROX index at the 12th hour comes into prominence for the continuance of the HFNC therapy. It should be confirmed by larger prospective studies. A

dynamic assessment of the ROX index would be appropriate in determining the treatment failure decision to avoid the problems of delayed intubation.

Ethics Committee Approval: Trakya University Clinical Research Ethics Committee (TÜTF-BAEK 2021/275) date of approval: 12.07.2021.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept- P.H., A.U., B.Y., V.İ.; Design- P.H., A.U., B.Y., V.İ.; Analysis or Interpretation- P.H., A.U., B.Y., V.İ.; Writing- P.H., A.U., B.Y., V.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: The authors declared that this study received no financial support.

Supplementary: http://balkanmedicaljournal.org/uploads/pdf/2022-6-31-supplementarymaterials.pdf

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