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The Relationship Between ROX Index and Inflammatory Markers In COVID-19 Patients

Jorge Martinez[1], Francesca Martinez-Nachon[1,2], Sammy Ghaoui[2], Paloma A. Molina[2], Adela Bazbaz[2], Romina Flores[2], Joseph Varon[2–4]

Abstract

Background: The ROX index is a bedside measure used to assess respiratory status during noninvasive oxygen support, but its relationship with inflammatory burden in COVID-19 remains incompletely characterized. This study evaluated the association between early ROX values and inflammatory markers in hospitalized adults with COVID-19 receiving high-flow nasal cannula (HFNC) or bilevel positive airway pressure (BPAP).

Methods: This retrospective single-center cohort included 994 adults hospitalized with COVID-19 between 2020 and 2022. Primary analyses were limited to patients with documented ROX values at 2, 6, or 12 hours after HFNC or BPAP initiation. Spearman correlation was used to assess the association between ROX and the highest in-hospital values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), d-dimer, interleukin-6 (IL-6), interleukin-10 (IL-10), ferritin, lactate dehydrogenase (LDH), white blood cell count (WBC), fibrinogen, and neutrophil-to-lymphocyte ratio (NLR). Exploratory secondary analyses examined correlations with ICHIKADO score, APACHE score, SOFA score, hospital length of stay, invasive mechanical ventilation duration, and clinical outcome.

Results: During HFNC, lower ROX values were significantly associated with higher ferritin, ESR, d-dimer, LDH, and WBC at 2 hours; higher ESR, IL-6, LDH, NLR, and WBC at 6 hours; and higher IL-6, LDH, NLR, and WBC at 12 hours. During BPAP, lower ROX correlated with d-dimer at 2 hours and with ferritin and d-dimer at 6 hours, whereas no significant inflammatory-marker association was observed at 12 hours. CRP, fibrinogen, and IL-10 were not significantly associated with ROX at any time point. Lower HFNC ROX values also correlated with higher ICHIKADO, SOFA, and APACHE scores, and lower ROX values in both HFNC and BPAP groups were associated with worse clinical outcome.

Conclusions: In this retrospective cohort, lower early ROX values were associated with greater inflammatory burden and higher illness severity, particularly among patients receiving HFNC. These findings should be interpreted as associative rather than predictive and warrant prospective validation with serial biomarker sampling, standardized outcome definitions, and multivariable adjustment.

Keywords: COVID-19, ROX index, high-flow nasal cannula, BPAP, inflammatory markers, respiratory failure, critical illness, prognostic markers

[1.] Universidad Popular Autónoma del Estado de Puebla, Puebla, México
[2.] Dorrington Medical Associates, Houston, Texas, USA
[3.] Independent Medical Alliance, Washington, D.C., USA
[4.] The University of Houston College of Medicine, Houston, USA

Corresponding author:
Joseph Varon, MD, FACP, FCCP, FCCM, FRSM
2219 Dorrington Street, Houston, Texas 77030, USA
Tel: +1-713-669-1670
Fax: +1-713-669-1671
Email: jvaron@imahealth.org

Introduction

The ROX index, which incorporates oxygenation and respiratory rate, has emerged as a practical bedside metric in acute hypoxemic respiratory failure and has been studied extensively in patients supported with high-flow nasal cannula. (1,2) In COVID-19, the index has drawn interest because it can be obtained repeatedly without invasive testing and may provide an early physiologic snapshot during noninvasive respiratory support. (2)

Severe COVID-19 is characterized not only by hy-

poxemic respiratory failure but also by a dysregulated inflammatory and thromboinflammatory response. Elevated concentrations of ferritin, IL-6, LDH, d-dimer, and leukocyte abnormalities have repeatedly been linked to greater disease severity, organ dysfunction, and mortality. (3–8) These laboratory abnormalities reflect overlapping processes such as tissue injury, endothelial dysfunction, immune activation, and coagulopathy.

Although both ROX and inflammatory biomarkers have been studied in COVID-19, the relationship between early ROX measurements and subsequent inflammatory burden has not been well described. Most prior ROX literature has focused on respiratory support success or failure, especially during HFNC therapy, rather than on how ROX relates to biochemical markers of systemic illness. (1,2)

The primary objective of this study was to evaluate the association between early ROX values and inflammatory markers in hospitalized adults with COVID-19 receiving HFNC or BPAP. The secondary exploratory objective was to examine whether ROX values were also associated with severity indices and hospital outcome. We hypothesized that lower early ROX values would be associated with greater inflammatory burden and more severe clinical illness.

Methods

Study design and population

This retrospective single-center cohort included 994 adults hospitalized with COVID-19 in Houston, Texas, between 2020 and 2022. The full cohort was used to describe baseline clinical characteristics. The primary ROX analyses were limited to patients who received HFNC or BPAP and had a documented ROX measurement at 2, 6, or 12 hours after initiation of the corresponding support modality. Because the study was retrospective, the number of observations varied across time points according to data availability.

The manuscript was revised to focus on association rather than predictive discrimination. Intubation was not analyzed as a formal primary endpoint in the present study, and no claims regarding independent prediction, discrimination, or causality were made on the basis of correlation analyses alone.

Data collection

ROX values were recorded at 2, 6, and 12 hours for patients receiving HFNC or BPAP. The available clinical dataset also included age, sex, race, body mass index (BMI), days hospitalized, clinical outcome, highest APACHE score, highest SOFA score, ICHIKADO score, type of noninvasive respiratory support before invasive mechanical ventilation, and number of days on invasive mechanical ventilation.

Inflammatory markers were collected from admission and discharge records, and the highest and lowest in-hospital values were recorded for each marker. The biomarkers evaluated in this study were CRP, ESR, d-dimer, IL-6, IL-10, ferritin, LDH, WBC, fibrinogen, and NLR. For the primary analysis, ROX values were compared with the highest recorded value of each biomarker during hospitalization. This approach was intended to reflect maximal inflammatory burden; however, because biomarker peaks could occur after the ROX measurement, the analysis was considered exploratory and associative rather than temporally predictive.

Statistical analysis

Continuous variables were summarized using means with standard deviations or medians with interquartile ranges, as appropriate. Categorical variables were summarized as frequencies and percentages. The primary analysis used Spearman's rho to examine the association between ROX and peak inflammatory-marker values. Exploratory secondary analyses used Spearman's rho to examine associations between ROX and ICHIKADO, highest APACHE score, highest SOFA score, length of stay, and invasive mechanical ventilation duration.

ROX values were also compared according to clinical outcome using the Mann-Whitney U test. Analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Complete-case analysis was used for each comparison. Because the study was exploratory, no multiple-comparison correction or multivariable modeling was applied.

Results

Cohort characteristics and ROX availability

The full cohort included 994 hospitalized adults with COVID-19. The median age was 56 years (interquartile range [IQR] 44–67), the median BMI was 29.3 kg/m² (IQR 25.8–34.5), and the median hospital length of stay was 7 days (IQR 4–12). The median highest APACHE score was 10 (IQR 7–17), the median highest SOFA score was 2 (IQR 2–5), and the median ICHIKADO score was 150 (IQR

120–200).

ROX values were available for HFNC at 2, 6, and 12 hours in 184, 183, and 195 patients, respectively, and for BPAP at the same time points in 105, 106, and 102 patients, respectively. Median ROX values in the HFNC group were 5.61 (IQR 4.31–8.30) at 2 hours, 5.82 (IQR 4.12–7.84) at 6 hours, and 5.85 (IQR 4.25–8.08) at 12 hours. The corresponding BPAP median values were 4.32 (IQR 3.30–5.03), 3.94 (IQR 3.20–5.54), and 3.93 (IQR 3.03–5.42), respectively (**Figure 1**).

Association between ROX and inflammatory markers

In the HFNC subgroup, lower ROX values were significantly associated with greater inflammatory burden across multiple biomarkers. At 2 hours, ROX correlated inversely with highest ferritin (r_s = -0.200, p = 0.007), ESR (r_s = -0.167, p = 0.024), d-dimer (r_s = -0.239, p = 0.001), LDH (r_s = -0.292, p < 0.001), and WBC (r_s = -0.185, p = 0.012). At 6 hours, significant inverse correlations were observed with ESR (r_s = -0.199, p = 0.007), IL-6 (r_s = -0.189, p = 0.015), LDH (r_s = -0.231, p = 0.008), NLR (r_s = -0.156, p = 0.034), and WBC (r_s = -0.149, p = 0.044). At 12 hours, ROX remained inversely associated with IL-6 (r_s = -0.197, p = 0.009), LDH (r_s = -0.315, p < 0.001), NLR (r_s = -0.171, p = 0.017), and WBC (r_s = -0.195, p = 0.006).

In the BPAP subgroup, the inflammatory associations were fewer. ROX at 2 hours was inversely associated with d-dimer (r_s = -0.202, p = 0.038), and ROX at 6 hours correlated inversely with ferritin (r_s = -0.224, p = 0.022) and d-dimer (r_s = -0.206, p = 0.034). No significant inflammatory-marker association was observed for BPAP ROX at 12 hours. CRP, fibrinogen, and IL-10 were not significantly associated with ROX at any measured time point in either modality (**Figure 2**). Overall, the number of significant inflammatory-marker associations was greater in the HFNC subgroup than in the BPAP subgroup, with the most frequent associations observed during HFNC at 2 and 6 hours (**Supplementary Figure A**).

Association between ROX, clinical severity, and hospital outcome

ROX values were also inversely associated with markers of clinical severity. In the HFNC subgroup, ROX at 2 hours correlated with ICHIKADO score (r_s = -0.263, p = 0.001), highest SOFA score (r_s = -0.253, p = 0.001), highest APACHE score (r_s = -0.260, p < 0.001), and days hospitalized (r_s = -0.188, p = 0.011). Similar inverse associations with ICHIKADO, SOFA, and APACHE scores persisted at 6 and 12 hours. In the BPAP subgroup, ROX showed fewer severity associations, although lower ROX at 6 and 12 hours correlated with a longer duration of invasive mechanical ventilation. A summary of these severity-related correlations is provided in **Supplementary Figure B**.

Clinical outcome analyses showed lower ROX ranks among patients with a worse hospital outcome at each time point. In the HFNC subgroup, outcome differences were significant at 2 hours (p = 0.003), 6 hours (p = 0.034), and 12 hours (p = 0.010). In the BPAP subgroup, the same pattern was observed at 2 hours (p = 0.018), 6 hours (p = 0.027), and 12 hours (p = 0.001) (**Figure 3**).

Discussion

This study found that lower early ROX values were associated with greater inflammatory burden and more severe clinical illness in hospitalized adults with COVID-19 receiving noninvasive respiratory support. The most consistent associations were observed in the HFNC subgroup, where lower ROX values correlated with higher LDH, d-dimer, ferritin, ESR, IL-6, WBC, and NLR, as well as with higher ICHIKADO, SOFA, and APACHE scores. Across all ROX assessments, LDH, WBC, and d-dimer showed the most consistent associations, whereas CRP, fibrinogen, and IL-10 were not significantly associated with ROX at any time point (**Supplementary Figure C**). In the BPAP subgroup, the associations were less extensive, although lower ROX values still related to selected inflammatory markers and worse hospital outcome.

These findings are broadly consistent with prior work showing that the ROX index captures clinically relevant information in acute hypoxemic respiratory failure and COVID-19. (1,2) However, whereas prior ROX studies primarily emphasized HFNC success or failure thresholds, the present analysis focused on how early ROX measurements relate to laboratory markers of systemic illness. In that sense, this study extends the bedside relevance of ROX beyond respiratory support monitoring alone.

The observed biomarker pattern is biologically plausible. ROX integrates oxygenation and respiratory rate, so lower values may reflect worsening gas exchange and increased work of breathing. In severe COVID-19, elevated IL-6, ferritin, LDH, d-dimer,

and leukocyte derangements are linked to hyperinflammation, tissue injury, endothelial activation, and coagulopathy. (3–8) The repeated inverse association between ROX and LDH, d-dimer, ferritin, and IL-6 therefore suggests that worse bedside respiratory physiology parallels a greater systemic inflammatory burden. At the same time, the absence of significant associations for CRP, fibrinogen, and IL-10 in this dataset may reflect differences in biomarker kinetics, treatment effects, or incomplete sampling rather than the absence of biologic relevance.

From a clinical perspective, these results support ROX as a useful physiologic adjunct that can be interpreted alongside inflammatory laboratory data in hospitalized patients with COVID-19. Nevertheless, correlation alone is insufficient to establish predictive performance or to justify specific decision thresholds. This study did not include ROC analysis, sensitivity/specificity estimates, calibration, or multivariable adjustment; therefore, the findings should not be interpreted as proof that ROX independently predicts intubation, mortality, or treatment response.

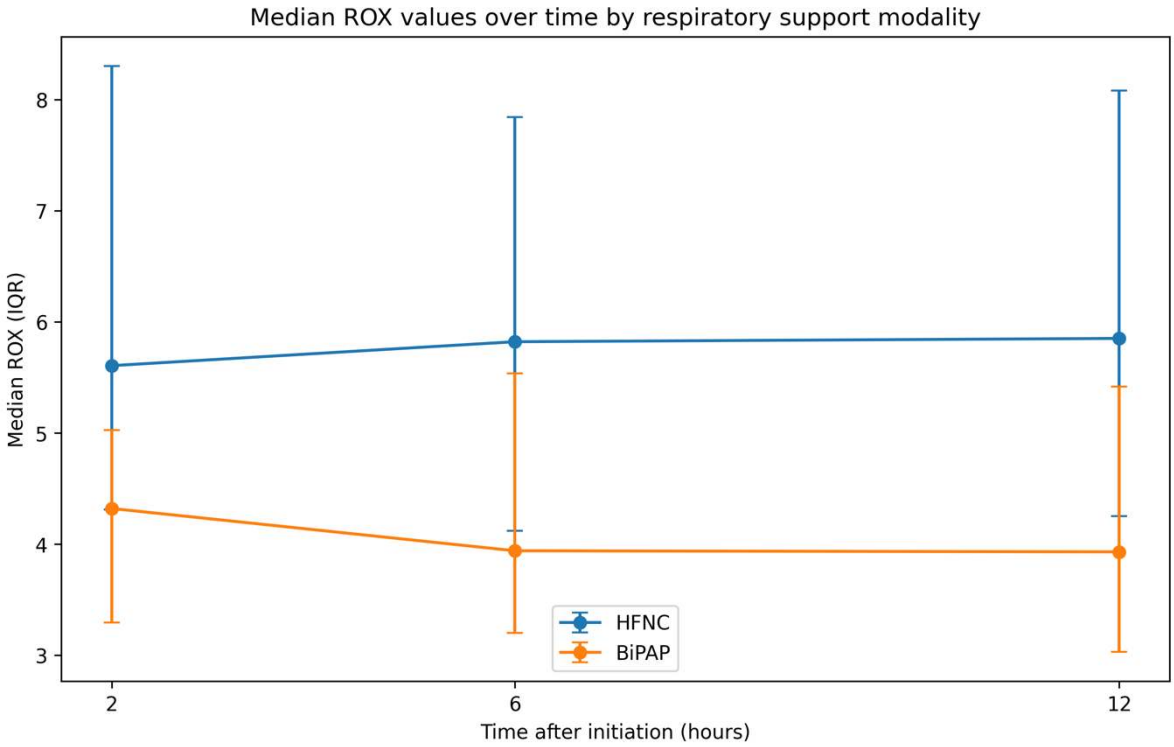
Several limitations should be acknowledged. First, the study was retrospective and conducted at a single center, which limits generalizability. Second, only a subset of the overall cohort had ROX measurements recorded at the prespecified time points, creating the possibility of selection bias. Third, the analysis compared early ROX values with peak in-hospital biomarker values, which introduces a temporal mismatch and limits causal or prognostic interpretation. Fourth, missing data were handled by complete-case analysis, and no multivariable model was used to adjust for potential confounders such as age, BMI, comorbidity burden, or baseline illness severity. Fifth, no multiple-comparison correction was applied because the analyses were exploratory. Finally, the study was not designed to evaluate standardized intubation criteria as a formal endpoint.

Future prospective studies should combine serial ROX assessments with contemporaneous biomarker sampling, standardized escalation criteria, and multivariable modeling to determine whether ROX adds independent prognostic information beyond established clinical severity measures. External validation in multicenter cohorts would also clarify whether the stronger pattern observed during HFNC is reproducible.

Conclusion

In this retrospective single-center cohort, lower early ROX values were associated with greater inflammatory burden, higher illness severity, and worse hospital outcome among adults hospitalized with COVID-19 receiving noninvasive respiratory support, particularly HFNC. These findings should be interpreted as associative rather than predictive and support further prospective studies with serial biomarker sampling and multivariable analysis.

Figure 1. Median ROX values at 2, 6, and 12 hours in patients receiving HFNC and BPAP



Legend: Error bars represent the interquartile range.

Figure 2. Heatmap of significant Spearman correlations between ROX and peak inflammatory markers across HFNC and BPAP time points

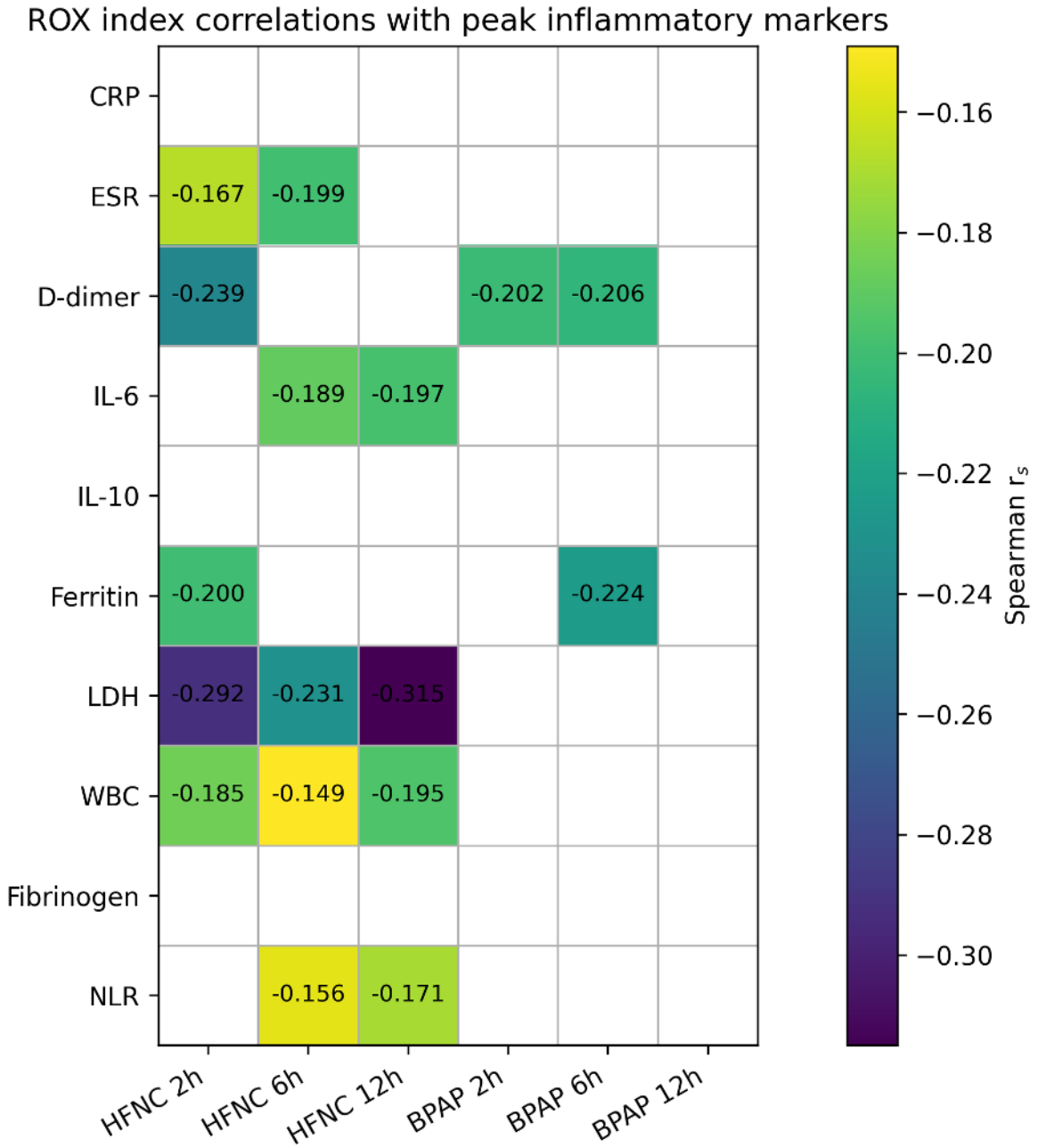
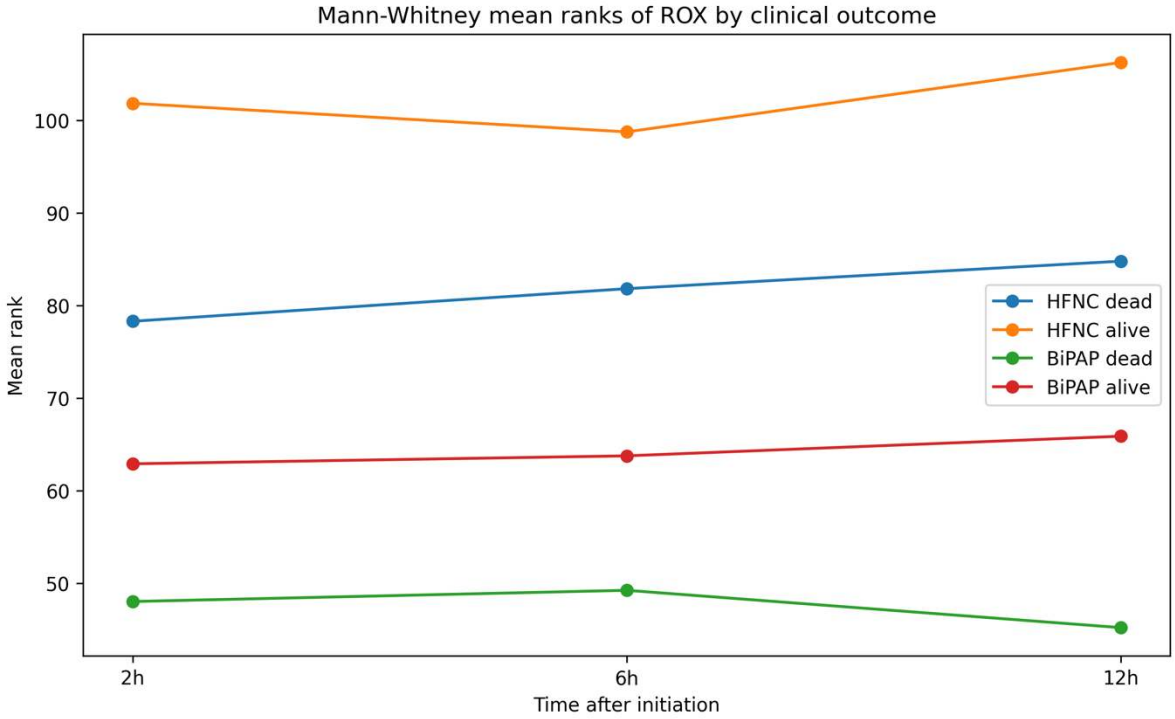


Figure 3. Mean-rank differences in ROX values by clinical outcome at 2, 6, and 12 hours in patients treated with HFNC or BPAP



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