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The Role of the Respiratory Rate Oxygenation (ROX) Index in the Early Identification of High-Risk Severe Acute Respiratory Infection (SARI) Patients Caused by COVID-19

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Abstract

Aim: This study aims to investigate the predictive value of the respiratory rate oxygenation (ROX) index for intubation and mortality in patients hospitalized with severe acute respiratory infection (SARI) caused by Coronavirus Disease 2019 (COVID-19), highlighting its potential for early risk stratification.

Study Design: A retrospective cohort study was conducted, including patients aged ≥18 years diagnosed with COVID-19-induced SARI. Statistical analysis was performed using Stata 15.1 software.

Results: The study comprised 53 patients (36 males and 17 females) with a median age of 60 years (range: 20-95). The median ROX index during hospitalization was significantly lower in patients who died compared to those who survived (3.93 vs. 10.08, p=0.0006). Additionally, the ROX index of intubated patients was notably lower than those who did not require intubation (3.93 vs. 9.39, p=0.0018).

Conclusions: The ROX index is an effective tool for the early identification of high-risk patients with SARI caused by COVID-19 who are at increased risk of intubation and mortality. This score can be used to predict high-risk patients in pandemic circumstances.

Keywords: Coronavirus Disease 2019 (COVID-19); Respiratory rate oxygenation (ROX) index; Triage; Intubation.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been spreading rapidly since late 2019, causing a pandemic worldwide. The World Health Organization named the disease Coronavirus Disease 2019 (COVID-19).[1] Despite advancements in vaccine development and drug treatments, the number of COVID-19 cases and fatalities worldwide continues to rise. Studies indicate that up to 20% of individuals infected with SARS-CoV-2 develop severe illnesses requiring hospitalization.[2,3]

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The COVID-19 pandemic has imposed an unprecedented burden on healthcare systems globally. Patients with severe acute respiratory infection (SARI) caused by COVID-19 often require respiratory support, including high-flow nasal oxygen (HFNO) or mechanical ventilation. Early identification of patients at high risk for intubation or mortality is critical to optimize resource allocation and improve patient outcomes.

The COVID-19 pandemic has significantly increased the workload and capacity requirements of hospital wards and intensive care units (ICUs). Hospital overcrowding, staff shortages, and the implementation of strict transmission precautions may delay the identification of patients whose clinical condition deteriorates during the pandemic due to the limited number of bedside visits.

Patients' conditions can deteriorate rapidly and undetected within hours, and delayed intubation often leads to increased mortality. By identifying laboratory values or basic respiratory indicators at the time of admission that predict high-risk patients, healthcare providers can reduce workload and improve survival rates. Although clinical risk scores such as the National Early Warning Score 2 (NEWS2), the quick Sequential Organ Failure Assessment (qSOFA), the Systemic Inflammatory Response Syndrome (SIRS) criteria, and the CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, and age ≥65) Pneumonia Severity Assessment are widely used, there is currently no evidence supporting their application in COVID-19 patients.[4] To address the difficulties faced by Severe Acute Respiratory Infection wards during the pandemic, there is an urgent need for effective tools to identify patients at risk of severe disease and guide clinical decision-making.

The respiratory rate oxygenation (ROX) index is defined as the ratio of peripheral oxygen saturation (SpO2) divided by the fraction of inspired oxygen (FiO2) (%) to the respiratory rate (breaths per minute). In a prospective observational cohort study involving patients with pneumonia or acute respiratory distress syndrome (ARDS) admitted to the ICU and treated with a high-flow nasal cannula, Roca et al.[5] described the ROX index in 2016. The ROX index, however, has only been validated in individuals with pneumonia-associated acute hypoxemic respiratory failure (AHRF). A notable clinical feature of COVID-19 is that, despite severe hypoxemia and cyanosis, a significant percentage of patients do not exhibit symptoms of respiratory failure or shortness of breath. These individuals, however, often bypass expected clinical phases and may develop ARDS, which can result in cardiac arrest and death.[6] This phenomenon is referred to as silent or happy hypoxia.[7] While severe pneumonia is the most common cause of AHRF, it is uncertain to what extent the same ROX cut-off values can be applied to other AHRF etiologies. Furthermore, in COVID-19 patients, silent hypoxemia may limit the safe use of the ROX index.

This study examines the predictive value of the ROX index for intubation and mortality in patients with SARI caused by COVID-19, aiming to contribute to the body of evidence supporting early risk stratification in this population.

Materials and Methods

This study is a retrospective analysis of data from patients admitted to the pulmonary SARI wards of our University Hospital between March and June 2020. Data were collected from 53 patients aged 18 years or older who met the criteria for SARI. Patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) test result were included in the study. Individuals whose imaging findings were consistent with COVID-19 but had a negative PCR test result were excluded. The study was approved by Marmara University Ethics Committee (Approval Number: 09.2020.291, Date: 27.04.2020), and the Ministry of Health's Scientific Research Committee.

COVID-19 patients admitted to our hospital were categorized as outpatients, patients requiring hospitalization, patients to be monitored in the SARI ward, and patients to be monitored in the ICU. These patients were managed and treated by physicians specializing in infectious diseases, chest diseases, and critical care in their respective departments.

The need for hospitalization in a patient who had developed an acute respiratory tract infection within the previous 14 days was classified as SARI if accompanied by fever, cough, dyspnea, tachypnea, hypoxemia, hypotension, significant radiological abnormalities on lung imaging, or changes in consciousness.[8]

COVID-19 therapy for these patients was administered in accordance with the Ministry of Health Guidelines in effect during the study period. Treatments included hydroxychloroquine, azithromycin, favipiravir, and tocilizumab, along with anticoagulant and supportive therapies as recommended.[9]

For hypoxemic patients, oxygen therapy was initially administered with a target SpO2 of 94%. Once stabilized, continuous oxygen therapy was titrated to achieve an SpO2 target of 90%. To maintain the desired oxygen saturation in SARI patients, the lowest FiO2 was utilized.

If the targeted oxygen saturation could not be achieved through current treatments or in other indicated cases, supplemental oxygen was administered using nasal cannulas, oxygen masks, oxygen masks with reservoirs, high-flow nasal cannula (HFNC), noninvasive mechanical ventilation, or invasive mechanical ventilation.

When low-flow oxygen therapies failed to provide adequate oxygenation and increased respiratory effort persisted, high-flow oxygen therapies were initiated.[10]

If no contraindications were present, noninvasive mechanical ventilation was utilized for patients experiencing increased respiratory distress, tachypnea, dyspnea, persistent hypoxemia, use of accessory respiratory muscles, or hypercarbia while on high-flow oxygen therapy.[11] Acute respiratory distress syndrome and septic shock treatments were administered according to international guidelines.[12] Patients were referred to the ICU if noninvasive oxygen support was inadequate, if cardiopulmonary resuscitation was required due to respiratory or cardiac arrest, or if septic shock necessitating vasopressor support was identified.

Patient information was retrieved from our hospital's electronic medical records system. Data recorded included age, gender, presenting symptoms, comorbidities, laboratory results at the time of admission, oxygen saturation measured via fingertip at admission, respiratory rate, and medications administered.

The ROX index, calculated as SpO2/(FiO2 x Respiratory Rate), was documented at the time of the patients' initial admission to the SARI wards. During follow-up, patients' vital signs were monitored at regular intervals; however, these values were not recorded.[5]

This study was conducted in accordance with the Declaration of Helsinki. No artificial intelligence-supported technologies were utilized in the study.

Statistical Analysis

Statistical analysis was performed using Stata 15.1 software (Statacorp, 4905 Lakeway Drive, College Station, Texas 77845, USA). The histogram, normal quantile plot, skewness-kurtosis test, and Kolmogorov-Smirnov test were used to assess whether numerical data followed a normal distribution. Median values, interquartile ranges, and minimum and maximum values were reported for numerical variables that did not have a normal distribution. Categorical variables were expressed as frequencies and percentages. The Mann-Whitney U test and Kruskal-Wallis test were employed to evaluate differences in the distribution of numerical variables across two or more groups. Categorical data were analyzed using chi-square and Fisher's exact tests. To predict intubation, receiver operating characteristic (ROC) analysis was used to determine a threshold value for 1/ROX values. The area under the curve (AUC) values were reported with 95% confidence intervals. Additionally, the sensitivity, specificity, accurate classification rate, and positive and negative predictive values of the threshold values were calculated. A p value of 0.05 or less was considered statistically significant.

Results

The characteristics of the study participants are summarized in Table 1. A total of 53 patients were included in the study, consisting of 36 males (67.92%) and 17 females (32.08%). The relationships between laboratory parameters and mortality are shown in Table 2. Among the laboratory parameters, lactate dehydrogenase (LDH), lymphocyte count, and lymphocyte percentage were found to be associated with mortality.

Table 1. Baseline characteristics of study participants

Characteristic	N	Value[1]
Age, years	53	60 (22)
Min-Max		25-95
Gender		
Male	36	67.92%
Female	17	32.08%
Length of stay, days	53	7 (11)
Min-Max		1-37
Comorbidities		
Hypertension	22	41%
Diabetes	16	30%
Chronic heart failure	9	16.9%
Chronic kidney disease	5	9.4%

[1]For continuous variables, the value represents the median with the interquartile range (IQR) in parentheses. For categorical variables, the value represents the count with the percentage of the total sample in parentheses. *Values in the "Min-Max" column indicate the minimum and maximum observed values for the respective variable.

Table 2. Relationships between laboratory parameters and mortality

Laboratory Test	N	Median (IQR)[1]	Range[2]	p[3]
D-Dimer				0.1549
Deceased	14	1.99 (1.87)	0.62-11.27	
Discharged	39	1.28 (2.43)	0.28-16.58	
Total	53	1.49 (2.18)	0.28-16.58	
C-reactive protein (mg/dL)				0.5929
Deceased	14	128.5 (122)	45-303	
Discharged	39	135 (119)	3-303	
Total	53	135 (110)	3-303	
LDH				0.0359**
Deceased	14	531 (145)	236-1303	
Discharged	39	380 (242)	222-808	
Total	53	448 (229)	222-1303	
Ferritin				0.7432
Deceased	13	666 (957)	116-2796	
Discharged	39	520 (661)	77-12010	
Total	52	570 (732)	77-12010	
Lymphocytes (n/mm³)				0.0006**
Deceased	14	450 (300)	0-1200	
Discharged	39	800 (400)	0-2100	
Total	53	700 (400)	0-2100	
Lymphocytes (%)				0.0142**
Deceased	14	5.55% (10.4%)	1.9%-33.8%	
Discharged	39	11% (11.1%)	1.5%-34.3%	
Total	53	10.4% (9.6%)	1.5%-34.3%	

[1]Median values are reported with interquartile ranges (IQR) in parentheses. [2]The "Range" column represents the minimum and maximum observed values for each variable. [3]P-values are provided to compare groups, with statistically significant values denoted in bold. IQR: Interquartile range; LDH: Lactate dehydrogenase; mg/dL: Milligrams per deciliter; n/mm³: Newtons per cubic millimeter.

The ROX index was calculated at the time of admission by recording respiratory rate, fingertip oxygen saturation levels, and the oxygen treatments administered upon arrival at the SARI ward. Due to incomplete records of one or more of these parameters, the ROX index could not be calculated for six patients, limiting the study to 47 participants.

The median ROX index for 12 patients who were intubated during follow-up was 3.93 (interquartile range [IQR]: 4.415; minimum: 2.25, maximum: 9.9). For 35 patients who did not require intubation, the median ROX index was 9.39 (IQR: 7.12; minimum: 2.18, maximum: 23.33) (p=0.0018). At the time of admission, the ROX indices of intubated patients were lower than those of non-intubated patients, and this difference was statistically significant (Table 3).

Table 3. Respiratory rate oxygenation (ROX) indices of patients at admission categorized by intubation requirement and outcome status

Group	N	Median (IQR)	Range	p
Intubation status				0.0018**
Intubation	12	3.93 (4.415)	2.25-9.9	
No Intubation	35	9.39 (7.12)	2.18-23.33	
Total	47	7.79 (8.91)	2.18-23.33	
Outcome status				0.0006**
Deceased	14	3.93 (4.26)	2.25-9.9	
Discharged	33	10.08 (7.03)	2.18-23.33	
Total	47			

[1]Median values are reported with interquartile ranges (IQR) in parentheses. [2]The "Range" column represents the minimum and maximum observed values for each variable. [3]P-values are provided to compare groups, with statistically significant values denoted in bold.

Table 4. Performance of respiratory rate oxygenation (ROX) index values in predicting intubation

ROX Index	Cutoff Point	Sensitivity	Specificity	Correctly Classified	LR+	LR-
9.107	(≥0.1098)	91.67%	54.29%	63.83%	2.0052	0.1535
2.970	(≥0.3367)	41.67%	91.43%	78.72%	4.8611	0.6380

When the impact of the ROX index on survival was analyzed, the median ROX index of patients who died was 3.93 (IQR: 4.26; minimum: 2.25, maximum: 9.9), compared to 10.08 (IQR: 7.03; minimum: 2.18, maximum: 23.33) in patients who survived (p=0.0006) (Table 4).

In the ROC analysis conducted to determine the ROX index cut-off point for predicting intubation, a value of 2.97% was identified as predictive of intubation with 91.43% specificity, 41.67% sensitivity, and 78.72% correct classification rate (CCR) (Figure 1). Intubation was required in 62.5% of patients with a ROX index of 2.97, while 37.5% were managed without intubation (p=0.018) (Figure 1). Only 5% of patients with a ROX index greater than 9.1 required intubation, whereas 95% were managed without intubation, a statistically significant finding (p=0.007).

Discussion

This study demonstrated that the ROX index, calculated at the time of admission, serves as a reliable predictor of the need for intubation and mortality in patients with COVID-19 hospitalized in the SARI service. This finding is significant in scenarios where resource limitations ex-

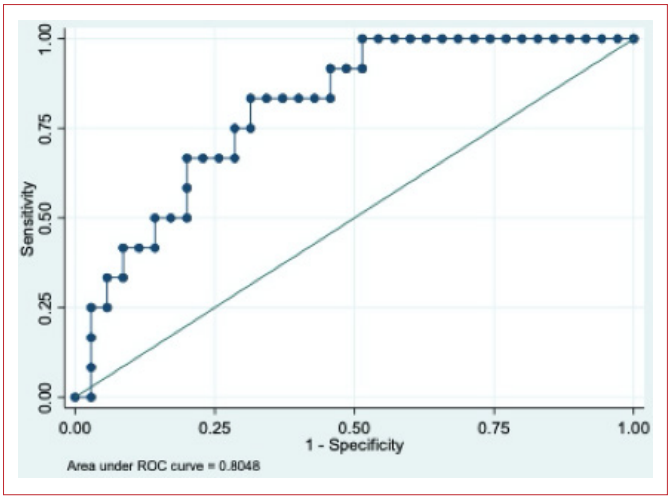

Figure 1. Respiratory rate oxygenation (ROX) index cut-off point to predict intubation.

ist, such as during the COVID-19 epidemic, as it can help identify patients who require intubation and intensive care early, enabling timely and effective allocation of resources and monitoring of high-risk patients.

The predictive performance of the ROX index in this study aligns with prior research on its application in non-COVID-19 respiratory diseases. By extending these findings to COVID-19-related SARI, our study underscores the importance of early identification of patients at risk for intubation and mortality.

The decision regarding the timing and strategy for intubation is inherently individualized and influenced by several factors, including patient selection, monitoring adequacy, and timely recognition of clinical deterioration. Delays in identifying high-risk patients can adversely affect outcomes. Therefore, it is essential to have objective methods for early identification of patients at high risk of deterioration during their hospital course. The ROX index is a simple, effective tool for this purpose, utilizing variables directly associated with oxygenation and respiratory distress.[5] Given that the variables required to calculate the ROX index are non-invasive, easy to obtain, and reproducible, it serves as a practical tool for clinical use. The ROX index has been used to evaluate the overall performance of HFNC therapy. A unique aspect of our study is that the ROX index was calculated at the time of admission to the SARI service, regardless of the patients' oxygen support systems. This study aimed to assess whether the ROX index could predict intubation and mortality.

Roca et al.[5] were the first to demonstrate that a ROX score of 4.88 predicts the success of HFNC therapy in ICU patients with pneumonia. In our research, the ROX cut-off value accurately predicted both mortality and the need for intubation, consistent with findings from previous studies. A cut-off value of 2.97 was identified as the most accurate for predicting intubation in our investigation. This lower value, compared to the cut-off value in other studies, may be attributed to its calculations shortly after the patients' arrival at the SARI service. The value may be higher in calculations performed over longer durations, as the respiratory rate (RR) tends to decrease with patient rest. Furthermore, a significant number of our patients do not meet the criteria for ARDS.

While there is substantial literature on the utility of the ROX index in other respiratory conditions, such as pneumonia and ARDS, our study expands upon these findings by demonstrating its relevance in the early assessment of patients infected with SARS-CoV-2. Studies like that of Lee et al.,[13] which evaluated the ROX index in septic patients, have demonstrated its potential in predicting outcomes such as 28-day mortality. Similarly, the ROX index's role in triage decisions has been emphasized in studies such as that by Zaboli et al., where it was found to be a useful tool for predicting ARDS development in COVID-19 patients presenting with dyspnea in the emergency department.[14-17]

The ROX index appears to offer an excellent combination of accuracy, noninvasiveness, and efficiency, particularly in settings where a blood gas analyzer is unavailable. It can be used to evaluate patients upon admission to the SARI service based on their priority level. The ability to assess patient severity at admission and prioritize care accordingly can significantly enhance clinical management and improve patient outcomes. Our study suggests that incorporating the ROX index into the initial assessment of COVID-19 patients could provide valuable insights into their clinical trajectory and facilitate more informed decision-making regarding intubation and intensive care.

Our study has several limitations. First, it is a retrospective observational study. The small sample size and single-center design may limit the generalizability of the findings. It may also be worthwhile to investigate whether the same findings can be applied to a larger population of individuals with more severe clinical characteristics. Additionally, our study did not account for the precise FiO2 delivered to patients, which may have

varied depending on their oxygen support requirements. Some patients, particularly those with high respiratory demands, may have received suboptimal FiO2, potentially affecting their ROX index values. Furthermore, the study was conducted during the first wave of the COVID-19 pandemic, a time when knowledge of the disease and its management was still evolving, which may have influenced clinical practices and outcomes. Finally, while the ROX index is well-suited for clinical use, other predictive models may provide greater accuracy or be simpler to implement in certain clinical scenarios.

Conclusion

In conclusion, our study highlights the significant utility of the ROX index as an early predictor of intubation and mortality in patients with COVID-19 admitted to the SARI service. The identification of a ROX index cut-off value of 2.97 demonstrated a high level of specificity in predicting intubation, indicating its potential as a valuable clinical tool.

With its non-invasive nature, ease of use, and strong predictive ability, the ROX index has the potential to be highly effective in identifying individuals at risk of developing ARDS. Given its strong predictive ability, we recommend integrating the ROX index into the initial evaluation of COVID-19 patients to enhance clinical decision-making and optimize resource allocation.

Future studies should investigate the broader applicability of the ROX index in diverse clinical settings and explore its potential integration with other predictive models to further improve patient management.

Ethics Committee Approval: This study was approved by Marmara University Ethics Committee (Approval Number: 09.2020.291, Date: 27.04.2020).

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Informed Consent: This study was conducted retrospectively, and informed consent was not applicable.

Author Contribution: Concept – C.Y., C.I., D.K., B.B., S.O.Y., S.K., E.E.; Design – C.Y., C.I., D.K., B.B., S.O.Y., S.K., E.E.; Supervision – C.Y., E.E.; Materials – C.Y.; Data Collection and/or Processing - C.Y.; Analysis and/or Interpretation - C.Y., C.I., E.E.; Literature Review – C.Y., E.E.; Writing – C.Y., C.I., D.K., B.B., S.O.Y., S.K., E.E.; Critical Review – C.Y., E.E.

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