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ROX Index Predicts Failure of HFNO Therapy in Patients of COVID-19 Pneumonia with Type I Respiratory Failure

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Abstract **Original Research Article**

Background: In the first half of 2020 COVID-19 disease has already converted into a global pandemic. Various treatment options were being tried all over the world. The ROX index (Respiratory rate – Oxygenation), defined as the ratio of peripheral oxygen saturation and fraction of inspired oxygen, to respiratory rate, is a simple bedside test to predict failure of HFNO Therapy and need for MV. ***Aim*****:** The aim of the study was to evaluate the accuracy of the ROX index for Predicting the failure of HFNO Therapy and need for Intubation in Patients of COVID-19 Pneumoniawith type I respiratory failure. ***Methods*****:** An observational study of consecutive patients admitted in ICU of the department of Anesthesiology, critical care and pain management in Govt. Medical college Srinagar (J&K) over the period of six months with moderate tosevere type I respiratory failure treated with High Flow Nasal OxygenTherapy (HFNOT). One hundred and thirty four RT-PCR positive COVID-19 patients were enrolled. The following data were collected: medical history, clinical classification of COVID-19 infection, the ROX index measured daily and the outcome assessment. ***Results*****:** We performed this observational study on 134RT-PCR positive COVID-19 patients. 70 (52.23%) patients with moderate to severe COVID-19 infection were intubated, 60% of them third day of admission, only 35% patients with moderate COVID-19 infection required intubation. Presence of comorbidities was directly associated with ROX index. At intubation, median (min-max) of ROX and PO2/FiO2 ratio was 4.02 (2.99–5.10) and 88.10 (58–106.15), respectively. ROX 1, 2, 3 indices were significantly associated with intubation ($p < 0.001$ for each of them). COVID-19 clinical classification was significantly associated with intubation ($p < 0.001$). ***Conclusion***: ROX index is a valuable, noninvasive tool to evaluate patients with moderate to severehypoxemic respiratory failure in COVID-19 treated with HFNOT. ROX is a simple noninvasive promising tool for predicting discontinuation of high-flow nasal oxygen Therapy (HFNOT) and could be used in the assessment of progress and the risk of intubation in COVID-19 patients with pneumonia.

Keywords: ROX index, COVID-19, Pneumonia, HFNOT, intubation, mortality.

INTRODUCTION

High Flow Nasal Oxygen Therapy (HFNO Therapy) is increasingly used in the management of Acute Hypoxemic Respiratory Failure (AHRF), as well as during the outbreak of Corona virus disease (COVID-19) [1-3]. Failure of HFNO Therapymay cause delayed intubation and increased mortality in patients with AHRF.[4] Severe hypoxemia resulting from COVID-19 pneumonia is often associated with near normal respiratory system compliance, which is almost never seen in severe ARDS. However, COVID-19 pneumonia in most cases falls under the Berlin definition of ARDS [5, 6].

High flow nasal oxygen Therapy (HFNO Therapy) and continuous positive airway pressure (CPAP) are recognised treatments for hypoxaemic respiratory failure caused by community-acquired pneumonia (CAP) [7-9]. HFNOT and CPAP may represent definitive Therapy avoiding unnecessary MV or provide bridging respiratory support that offsets the need for immediate MV, preserving finite critical care resources. The ratio of oxygen saturation (ROX) index

is used to predict failure of HFNOT in treatment of CAP [8, 9]. There are little published data describing the use of ROX index to guide use of HFNO Therapy to treat COVID-19-associated respiratory failure; we provide further evidence to validate ROX index use in this setting [10, 11]. The ROX index was developed as a simple bedside test to predict failure of HFNO THERAPY and need for MV, although viral pneumonia patients were likely under-represented in derivation and validation studies [7].

Thus, the need for rapid and simple toolsto be able to support critical clinical decisions. For these reasons, the Authors tested the ROX index (Respiratory rate – OXygenation) which is defined as the ratio of peripheral oxygen saturation (SpO2) and a fraction of inspired oxygen (FiO2) to Respiratory Rate (RR). The ROX index was first described by Roca *et al*., in 2016 [12] in a bicentric prospective observational cohort study involving 157 patients with pneumonia/ARDS admitted to the intensive care unit (ICU) and treated with a high-flow nasal cannula (HFNO Therapy). It was shown that a ROX Index < 4.88, measured 12 h after HFNO Therapy onset, was related to a higher risk of intubation (sensitivity 70.1%, specificity 72.4%). The same results were found in a subsequent multicentric prospective observational study, designed to validate the diagnostic accuracy of the index, which enrolled 191 patients with pneumonia admitted to the ICU and treated with HFNO Therapy [13]. So, this study was planned to validate the diagnostic accuracy of the ROX index for COVID-19 pneumonia outcome (the need for intubation).

METHODS

This observational study of consecutive patients admitted in ICU of the department of Anesthesiology , critical care and pain management in Govt. Medical college Srinagar (J&K) over the period of six months with moderate to severe type I respiratory failure treated with High Flow Nasal OxygenTherapy (HFNOT). One hundred and thirty four RT-PCR positive COVID-19 patients were enrolled. The following data were collected: medical history, clinical classification of COVID-19 infection, the ROX index measured daily and the outcome assessment.

All patients with moderate to severe hypoxemic respiratory failure who were treated with HFNOT at any point during the stay in ICU were included in the study. Moderate and severe hypoxemic respiratory failure was defined as hypoxemia requiring more than 6 L/min of oxygen via nasal cannula.

Demographics including age, sex, comorbidities, body mass index (BMI), and smoking status (current smoker, non-smoker) were collected. In addition, laboratory biomarkers on admission including complete blood count (CBC) with differential, ferritin, fibrinogen, lactate dehydrogenase (LDH), D-dimer, and C-reactive protein (CRP) were analyzed. Respiratory metrics at the initiation of HFNOT included respiratory rate (RR), pulse oximetry, and fraction of inspired oxygen (FIO2). The same parameters were collected at days 1, 2, 3 and 5 post-initiation of HFNOT. Parameters were recorded at the lowest FIO2 and highest pulse oximetry reported for the day. For patients who required invasive mechanical ventilation (IMV) prior to the conclusion of data collection, respiratory parameters on the day of intubation were reported. Days on HFNOT, time to intubation (in days), average flow rate on HFNT, and the presence of hospital acquired pneumonia (HAP)/Ventilator associatedPneumonia (VAP) were also reported.

HFNOT was initiated with high flows of 50-60L/min, and adjusting FiO2 to maintain SpO2 between 92- 96%. The temperature was targeted according to patient comfort. The patients were monitored by non-invasive measurement of heart rate and blood pressure, oxygen saturation and respiratory rate. FiO2 was gradually reduced keeping the target SaO2. Flow was also gradually decreased according to the patient's tolerance and reduction of respiratory rate (RR). On the other hand, when patients could not sustain SpO2 or reduce RR, they were upgraded to NIV. If the patient's status deteriorated, she/he was guided for endotracheal intubation. HFNOT failure was defined as escalation to invasive mechanical ventilation (IMV) or death. The standard indications for endotracheal intubation (ETI) included the following: respiratory rate (RR) greater than 35 breaths/min, obvious accessory respiratory muscle activity or abdominal paradoxical breathing, progressive increase in PaCO2, hemodynamic instability and inability to protect the airways or inability to obtain saturation greater than 93% with FiO2 greater than 80%.

Statistical Methods

Continuous variables are presented as means (± standard deviation), and categorical variables as numbers and Frequency (percentages). Continuous variables were compared with the use of the two-sample t-test or paired t-test for categorical variables with the use of the Pearson chi-square test.

To build a predictive model of the intubation, multivariable logistic regression was performed to determine the adjusted associations of the variables with intubation. The initial model included all the variables associated with intubation in univariate analyses for $p<0.1$. The final model that optimized the balance of the fewest variables with good predictive performance. Assessment of model performance was based on discrimination and calibration. Discrimination was evaluated using the C-statistic, which represents the area under the receiver operating characteristic (ROC) curve, where higher values represent better discrimination. Calibration was assessed by the Hosmer- Lemeshow test, where a p-value greater than

0.05 indicates adequate calibration. All statistical tests were two-tailed, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

In this observational study 134 patients included with mean age 51.52±12.88 in the Patients with moderate Covid-19 symptoms and 52.45±11 mean age among the Patients with Severe Covid- 19 symptoms. The demographic profile of the study population was comparable (Table 1). Most of the studied patients had Comorbidity. Hypertension was the most common Comorbidity among the study population fallowed by Asthma and COPD reported (Table 2). About 52% of the studied patients were intubated on different days of admission (Fig 1). At intubation, median (min-max) of ROX and PO2/FiO2 ratio was 4.02 (2.99–5.10) and 88.10 (58–106.15), respectively. ROX 1, 2, 3 indices were significantly associated with intubation ($p \leq 0.001$ for each of them). COVID-19 clinical classification was significantly associated with intubation ($p: \leq 0.001$) (Figure 2). Twenty five patients refused to give consent for intubation. Among those only seven patients survived.

Table 1: Demographic profile of the study population (134)

Parameter	Patients with moderate Covid- 19	Patients with Severe Covid- 19
NO. of patients	**64**	**70**
Age	**51.52±12.88**	**52.45±11.38**
Male/Female	**42/22**	**52/18**
Smokers/non smokers	**38/26**	**48/22**

Table 2: Comorbity among the study population

Comorbity	Patients with moderate Covid- 19	Patients with Severe Covid- 19
Hypertension	**23.4%**	**24.28%**
Diabetes mellitus	**10.93%**	**12.85%**
COPD	**20.31%**	**17.14%**
Asthma	**17.18%**	**14.28%**
Other respiratory diseases	**4.68%**	**7.14%**
Ischemic heart disease	**6.25%**	**5.71%**
Chronic kidney disease	**4.68%**	**8.57%**
Previous TIA/stroke	**7.81%**	**7.14**
Liver disease	**4.68%**	**2.85**

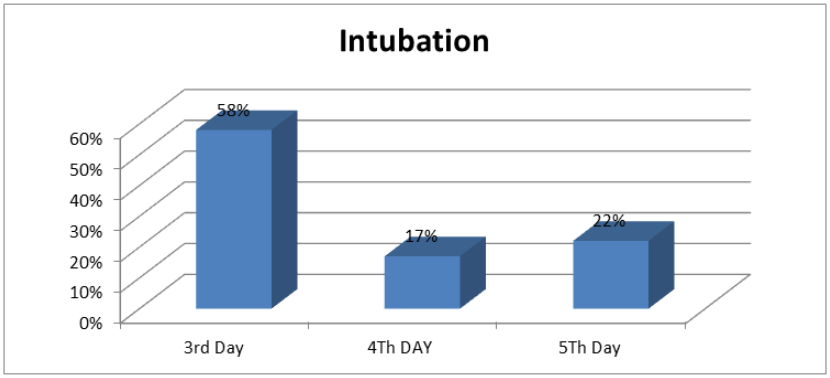

Fig 1: Days of intubation

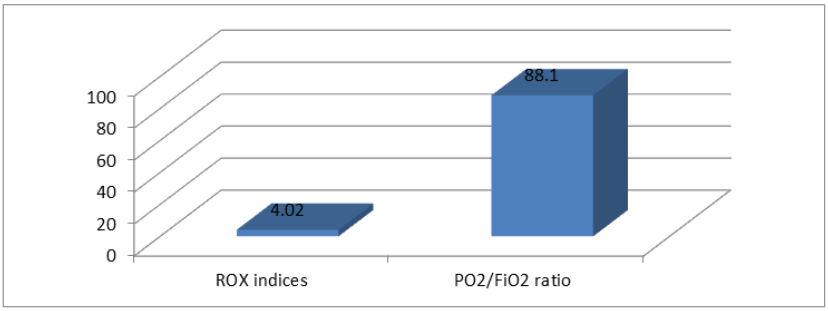

Fig 2: ROX and PO2/FiO2 ratio

DISCUSSION

The ROX index has been proposed as a tool to predict HFNOTout come in patients with AHRF, mainly admitted to the ICU. Delayed intubation has been shown to be associated with poor clinical outcome, so predicting the failure of noninvasive ventilation or oxygen Therapy has remained an important area of research [14]. One important concern during the management of COVID-19 pneumonia is not to delay intubation in patients with acute hypoxemic respiratory failure. An objective method to identify subjects who are likely to fail to respond to oxygen therapy is needed. The ROX index is remarkably simple and has the potential to become a routine parameter in clinical practice.

The ROX index is an easy-to-use tool which relies on variables directly linked to oxygenation (assessed by SpO2/ FiO2) and respiratory distress (assessed by RR), potentially leading to pump ineffectiveness. Due to the relationship between these variables, they can compound one another since patients with severe disease are more likely to have a lower SpO2/ FiO2 and a higher RR [15]. The variables required are noninvasive and are easily and quickly obtained, as well as being reproducible. The present study demonstrated the higher accuracy of the ROX index as compared to RR alone in the prediction of intubation.

Roca and colleagues [16, 17] first published an index ROX which can predict whether the patient will fail to use high frequency nasal cannula (HFNO Therapy) in pneumonia in ICU, and they reported that a ROX value of > 4.88 predicted the success of HFNO Therapy. Also, in Nicholas and Robin's study [18], the ROX index was validated in 191 critically ill patients enrolled at 5 centers in France and Spain, and the ROX index score of 4.88 was used as predictive of outcomes. The area under the curve at 12 hours of HFNO Therapy use was 0.752. Both studies calculated the ROX index at 0, 2, 6, 12 hours from the onset of oxygen therapy.

Rodriguez *et al*., [19] found that the ROX index in critically ill patients in ICU was higher in the subjects who were successfully separated from HFNO Therapy at the first trial than in those who failed (12.7 *vs* 10.2, $p = 0.002$). The ROX index ≥ 9.2 predicted successful separation from HFNO Therapy at the first trial (specificity of 50%, sensitivity of 84%, positive predictive value of 93%, negative predictive value of 30%, and accuracy of 80%). They calculated the ROX index up to 48 hours.

All previous studies were conducted on critically illpatients other than COVID-19. To the best of our knowledge, there is only one recent study done by Belz and coworkers [20] using the ROX index for monitoring of oxygen therapy by HFNO Therapy in a SARS-CoV-2 severe pneumonia admitted to ICU with proven COVID-19, and the authors found that performance characteristics of ROX at 0.5 hour using the previous published cut-off value of 4.88 by Roca and colleagues [15, 16] had a 81% sensitivity and a 38% specificity. In this study, we used the ROX index as a simple noninvasive tool in COVID-19 pneumonia patients for prediction of the need for intubation. In contrast to previous studies, the ROX index was measured daily as they collected data from different medical facilities that dealt with COVID-19 cases, and they found that all patients with severe COVID-19 infection (100%) were intubated, however, only 32% of moderate COVID-19 infection patients who needed oxygen therapywere intubated in our study. All persons with moderate COVID-19 infection were intubated on the 5th day of admission.

The results of multivariate logistic regression of predictors of intubation among COVID-19 patients have shown that female sex and ROX.1 (the ROX value on the first day of admission) are the only significant independent predictors of intubation in this study. Cut-off point of ROX.1 (the ROX value on the 1st day of admission) was ≤ 25.26 (90.2% of sensitivity and 75% of specificity) (AUC, p): (0.897, ≤ 0.001), ROX.2 (the ROX value on the 2nd day of admission) was ≤ 21.34 (90% of sensitivity and 75% of specificity) and of ROX.3 (the ROX value on the 3rd day of admission) ≤ 11.71 (90% of sensitivity and 100% of specificity). The cut-off value is higher than in other studies because we conducted this study on heterogeneous cases of different severities as we involved some less severe cases of moderately severe COVID-19 pneumonia. ROX.1 was significantly associated with the presence of comorbidities, COVID-19 clinical classification, CT findings, intubation ($p \leq 0.001$ for each of them). Also, there was a negative significant association with albumin.

Conflict of Interest: Nil

Funding: Nil

CONCLUSION

ROX index is a valuable, noninvasive tool to evaluate patients with moderate to severehypoxemic respiratory failure in COVID-19 treated with HFNOT. ROX is a simple noninvasive promising tool for predicting discontinuation of High-Flow Oxygen Therapy and could be used in the assessment of progress and the risk of intubation in COVID-19 patients with pneumonia.

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