

# Comparison of the Discrimination Capacity of the ROX and HACOR Scales to Predict High-flow Nasal Cannula Failure in Patients With SARS-CoV-2 Pneumonia

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## Research Article

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# Abstract

## Background

The pandemic of SARS-CoV-2 infection has created a challenge in health services worldwide. Some scales have been applied to evaluate the risk of intubation, such as the ROX and HACOR. The objective of this study is to compare the predictive capacity of the HACOR scale and the ROX index and define the optimal cut-off points.

## Methods

Study of diagnostic tests based on a retrospective cohort. Composite outcome was the proportion of patients that needed orotracheal intubation or died of COVID-19 pneumonia. Discrimination capacity was compared by the area under the curve of each of the two scales and the optimal cut-off point was determined using the Liu method.

## Results

245 patients were included, of which 140 (57.14%) required OTI and 152 (62.04%) had the composite end result of HFNC failure. The discrimination capacity was similar for the two scales with an AUROC of 0.71 and 0.72 for the HACOR scale for the ROX index, respectively. The optimal cut-off point for the ROX index was 5.62 (sensitivity 62% specificity 65%), while the optimal cut-off point for the HACOR scale was 5.5 (sensitivity 66% specificity 65%).

## Conclusions

The HACOR scale and the ROX index have a moderate predictive capacity to predict failures to the HFNC strategy. They can be used in conjunction with other clinical variables to define which patients may require invasive mechanical ventilation.

## Introduction

It is well known that about 16% of patients with severe COVID-19 pneumonia required intensive care (ICU) (1). Among them the rate of invasive mechanical ventilation (IMV) is between 71% and 90% (2), with mortality close to 50% (3)(4). There are different ways to deliver oxygen in patients with severe pneumonia such as high-flow nasal cannula (HFNC), standard oxygen therapy delivered through a face mask, or noninvasive positive-pressure ventilation (NIPPV). Although there was no significant difference between the requirement for orotracheal intubation in the different interventions, the number of ventilator-free days at day 28 was significantly higher in the high-flow-oxygen group (5). Therefore, the use of HFNC associated with the prone position (6)(7) is currently recommended for severe COVID-19 pneumonia as first-line treatment, since some patients can improve oxygenation and fatigue and avoid invasive mechanical ventilation with these strategies (8).

However, it is also known that the delay initiation of invasive mechanical ventilation (IMV) in patients with severe pneumonia leads to an increase in mortality (9), that is why it is so important to identify in a timely manner the patients in whom this therapy may fail. To do this, scales have been created to predict failure to non-invasive mechanical ventilation strategies (NIMV), including the ROX index, which consists of a relationship between arterial oxygen saturation / fraction of inspired oxygen ratio (SpO<sub>2</sub>/FIO<sub>2</sub>) and respiratory frequency. It was validated in 2016(10), as an index for predicting HFNC therapy failure in patients with severe pneumonia. Roca et al. (5) found that a score of 4.88 after 2 hours of HFNC therapy predicts failure to HFNC (AUC of 0.74). In addition, studies have been done that validate its usefulness in patients with COVID19 pneumonia (14,15,16,17). However, the main problem with the ROX scale lies in the delay in the initiation of IMV in people who require it.

In 2017, Jun Duan et al (8) created a tool called HACOR, an acronym for heart rate, acidosis, state of consciousness, oxygenation, and respiratory rate, to predict NIMV failure. In 2020, Carrilo et al (10) validated this tool with 2711 patients, showing that the HACOR scale accurately predicted NIV failure in the first hour. A cut-off value of 8 points at 1 h of HFNC beginning had a AUC greater than 0.9 for predicting NIV failure in patients with pneumonia and adult respiratory distress syndrome (ARDS). To our knowledge, the HACOR score has not been validated in patients with COVID19.

Although these scales have been validated in patients with severe pneumonia, we do not know if the HACOR scale is useful in patients with COVID19 and if its discrimination capacity is better than the ROX scale. The objective of this study is to compare the discrimination capacity between the HACOR and ROX scales to predict the risk of invasive mechanical ventilation in patients with severe SARS-COV2 pneumonia who are with HFNC strategy in the resuscitation unit of a hospital in Colombia.

## Methods

### Trial oversight

Study of diagnostic tests based on a retrospective cohort. We conducted the study in the emergency unit of a high complexity University Hospital in Bogota, Colombia. The study protocol was approved by the "Research and Institutional Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Javeriana, and the Hospital Universitario San Ignacio". Since the study was based on data collection, patient consent was not required. This waiver is given in agreement with the Helsinki declaration and resolution number 008430 of 1993 issued by the Ministry of Health from the Republic of Colombia.

The first investigator was responsible for searching the hospital's database, while the second investigator ensured adherence to the protocol. Tests were conducted in accordance with principles of the Helsinki Declaration. Authors assume responsibility for the integrity of the data and its analysis.

### Patients

Total adult population identified with viral pneumonia by SARS CoV2 that required HFNC in the emergency department of the San Ignacio Hospital, between August and December of 2020 were eligible for enrollment. Data were taken from patients older than 18 years of age who had the diagnosis of SARS CoV2, confirmed by polymerase chain reaction (PCR). Patients with SARS CoV2 pneumonia who had required immediate ventilatory support with invasive mechanical ventilation and patients with severe or refractory agitation to sedation, massive bronchial aspiration, inability to manage bronchial secretions were excluded.

## Trial Procedures

The decision to initiate a HFNC was made by the emergency physician or internist attending the patient, based on the following criteria: The clinical presentation of respiratory failure (such as the use of accessory muscles, breathing rate greater than 20 per minute, paradoxical abdominal movement, desaturation despite nasal cannula or venturi therapy), partial pressure of arterial oxygen (PaO<sub>2</sub>) less than < 60 mmHg or the PaO<sub>2</sub>/inspired fraction oxygen ratio < 300 with supplemental oxygen.

HFNC was managed by respiratory therapist professionals and patient's emergency physicians and internists, depending on the case. Masks, heated humidifiers, air-oxygen blenders, and cannulas (i.e., consumable materials) were owned by the Hospital. The device used as high-flow therapy was the HFNC AIRVO™ 2 Optiflow™ and the parameters at the beginning of the therapy were established according to the patient's last partial PaO<sub>2</sub>/FiO<sub>2</sub> to achieve a SaO<sub>2</sub> greater than 90%. Once respiratory failure improved, progressive decrease in the parameters of the HFNC were initiated. This was done when the patient had a breathing rate of fewer than 25 breaths per minute, without signs of muscle fatigue, had a SaO<sub>2</sub> greater than 90%, and PaO<sub>2</sub>/FiO<sub>2</sub> in ascent concerning that taken before the beginning of the HFNC. Oxygen Flow was always lowered initially and, according to the patient's tolerance, the inspired fraction of oxygen parameter was subsequently lowered. All patients underwent gasometric monitoring before the onset of HFNC. After 2 hours of HFNC therapy onset, vital signs, arterial blood gases and the HACOR and ROX scales were performed.

## Outcomes

Primary outcome was HFNC therapy failure, including need for mechanical ventilation onset and death associated with COVID-19 pneumonia.

## Statistical analysis

Demographic and epidemiological characteristics of patients diagnosed with COVID-19 pneumonia who required HFNC therapy were described.

According to the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement (TRIPOD) (11), the minimum sample size was 100 events and 100 not events, so a minimum of 100 failures to the HFNC was sought. The baseline characteristics were compared between the treatment groups with the use of chi-square and Wilcoxon tests.

The discrimination capacity of the HACOR and ROX scales was evaluated using the area under the receiver operating characteristic curve (ROC curve). The comparison of both scales was carried out by comparing the areas under the curve of the two scales. A secondary analysis of the ROX and HACOR scales was finally performed to predict failure of HFNC.

Finally, the Liu method was performed to identify the cut-off point with the best performance of the HACOR and ROX scales (12).

## Results

### Patient Characteristics

A total of 245 patients were included in the study. Most of them were men (65.3%). Mean ( $\pm$  SD) age of the patients was 62.53 ( $\pm$  13.83) years. A total of 93 patients (37.96%) were 18 to 60 years of age and 152 (62.04%) were 60 years of age or older. 152 (62.04%) patients had the final composite outcome of HFNC failure (requirement of orotracheal intubation or death by COVID19). Death associated with SARSCov2 infection occurred in 72 patients (29.39%).

Table 1 shows key characteristics of the patients, stratified into two groups according to whether the patient had the final composite outcome. Interestingly, there were clinically significant imbalances in baseline characteristics with respect to prior history of hypertension, atrial fibrillation, and chronic kidney disease (CKD) between both groups.

Table 1

Characteristics of patients according to HFNC failure (final composite outcome including requirement of orotracheal intubation or death by COVID19) \*

Characteristic	Failure to HFNC		P-value
	Yes n 152	No n 93	
Age, years Mean (SD)	64.16 (12.97)	59.88 (14.81)	<b>0.040</b>
Age Group, n (%)			<b>0.13</b>
< 40	6 (3.94)	11 (11.82)	
40–59	47 (30.92)	29 (31.18)	
60–79	83 (54.60)	46 (49.46)	
≥ 80	16 (10.52)	7 (7.53)	
Sex Male, n (%)	106 (69.73)	54 (58.06)	<b>0.073</b>
BMI † Mean (SD)	28.10 (5.29)	27.19 (5.01)	<b>0.080</b>
Diabetes Mellitus, n (%)	52 (34.21)	26 (27.96)	<b>0.33</b>
Atrial fibrillation, n (%)	17 (11.18)	2 (2.15)	<b>0.012</b>
CKD, n (%)	21 (13.81)	4 (4.30)	<b>0.017</b>
Heart failure, n (%)	21 (13.81)	5 (5.38)	<b>0.053</b>
ACS antecedent, n (%)	11 (7.23)	4 (4.30)	<b>0.42</b>
Hypertension, n (%)	90 (59.21)	38 (40.86)	<b>0.006</b>
Isolation (bacterial or viral different from SARSCoV2), n (%)	51 (33.55)	5 (5.38)	<b>&lt; 0.0001</b>
COPD, n (%)	21 (13.82)	17 (18.28)	<b>0.37</b>
CVA/TIA, n (%)	2 (1.32)	3 (3.23)	<b>0.37</b>
Dementia, n (%)	2 (1.32)	1 (1.08)	<b>1.0</b>
Cirrhosis, n (%)	1 (0.66)	1 (1.08)	<b>1.0</b>
Autoimmune disease, n (%)	4 (2.63)	4 (4.30)	<b>0.48</b>
Solid tumors, n (%)	12 (7.89)	4 (4.30)	<b>0.42</b>
Hematologic malignancy, n (%)	2 (1.32)	1 (1.08)	<b>1.0</b>
HIV, n (%)	0 (0)	1 (1.08)	<b>0.38</b>

	Failure to HFNC		
Heart rate, Mean (SD)	85.28 (16.47)	80.31 (15.00)	0.014
Glasgow coma score < 15 n (%)	55 (36.18)	8 (8.60)	< 0.0001
Respiratory rate, Mean (SD)	25.94 (5.72)	22.28 (3.53)	< 0.0001
HACOR, Mean (SD)	7.14 (3.62)	4.45 (2.23)	< 0.0001
ROX Index, Mean (SD)	5.61 (4.08)	6.63 (1..87)	< 0.0001
Death by SARS-CoV 2, n (%)	72 (47.36)	0 (0)	< 0.0001
Required OTI, n (%)	140 (92.11)	0 (0)	< 0.0001
* There were no significant differences ( $p < 0.05$ ) between the study groups.			
SD standard deviation. BMI denotes Body mass index, DM diabetes mellitus, CKD chronic kidney disease, HFNC High-flow nasal cannula. ACS Acute Coronary Syndrome, COPD chronic obstructive pulmonary disease, CVA Cerebrovascular accident, TIA transient ischemic attack, HIV human immunodeficiency virus, OTI Orotracheal intubation.			
† the body-mass index is the weight in kilograms divided by the square of the height in meters.			

In the HFNC failure group, the median age was 64,16 years ( $P = 0.04$ ). Also, In the group with HFNC failure, there was a significantly higher number of people with atrial fibrillation, chronic kidney disease and hypertension. Of the clinical and paraclinical variables taken prior to the initiation of the HFNC, the arterial pressure of Co<sub>2</sub> (PaCo<sub>2</sub>) had a statistical significance between the groups that did not fail and those that did fail HFNC (29.83 vs 31.44  $P = 0.014$ ), There were statistically significant differences at 2 hours after starting the HFNC strategy in the variables pH (7.43 vs 7.46  $P = 0.004$ ), SaO<sub>2</sub> (92% vs 95%  $P < 0.0001$ ), PaO<sub>2</sub> (78.10 vs 89.02  $P < 0.0001$ ), PaO<sub>2</sub> / Fio<sub>2</sub> (103.62 vs 133.23  $P < 0.0001$ ), Glasgow coma scale (14.18 vs 14.87  $P < 0.0001$ ) and respiratory rate (25 vs 22 Breaths per minute  $P < 0.0001$ ) (Table 2). The 2-hour ROX index was 6.63 and 5.61 for patients who did not fail and failed to HFNC, respectively ( $P < 0.0001$ ). The HACOR score was 4.45 and 7.14 for patients who did not fail and failed to HFNC at 2 hours, respectively ( $P < 0.0001$ ). The mean time to failure of the HFNC was 1.4 days ( $\pm 3.8$ ).

Table 2

Basal and two hours arterial gases after initiation of the HFNC, distributed according to HFNC failure (final composite outcome including requirement of orotracheal intubation or death by COVID19) \*

Characteristic	Failure to HFNC		P-value
	Yes	No	
pH <sup>a</sup> , Mean (SD)	7.45 (± 0.05)	7.45 (± 0.05)	<b>0.20</b>
PaO <sub>2</sub> <sup>a</sup> , Mean (SD)	72.49 (24.97)	73.14 (20.80)	<b>0.22</b>
PaCO <sub>2</sub> <sup>a</sup> , Mean (SD)	29.83 (6.41)	31.44 (7.20)	<b>0.014</b>
PaO <sub>2</sub> /Fio <sub>2</sub> <sup>a</sup> , Mean (SD)	111.61 (46.84)	121.82 (51.10)	<b>0.16</b>
SaO <sub>2</sub> <sup>b</sup> , Mean (SD)	92.04 (6.52)	95.03 (2.99)	<b>&lt; 0.0001</b>
pH <sup>b</sup> , Mean (SD)	7.43 (0.08)	7.46 (0.05)	<b>0.004</b>
PaO <sub>2</sub> <sup>b</sup> , Mean (SD)	78.10 (23.24)	89.02 (28.32)	<b>&lt; 0.0001</b>
PaCO <sub>2</sub> <sup>b</sup> , Mean (SD)	34.20 (10.91)	32.74 (7.08)	<b>0.80</b>
PaO <sub>2</sub> /Fio <sub>2</sub> <sup>b</sup> , Mean (SD)	103.62 (38.55)	133.23 (50.85)	<b>&lt; 0.0001</b>
* There were no significant differences (p < 0.05) between the study groups.			
a. Before HFNC			
b. 2 hours post HFNC.			
SD standard deviation. HFNC High-flow nasal cannula. SaO <sub>2</sub> blood-oxygen saturation, PaO <sub>2</sub> Arterial partial pressure of oxygen, PaCO <sub>2</sub> Partial pressure of carbon dioxide, Fio <sub>2</sub> fraction of inspired oxygen			

In univariate analysis (Table 3) the variables that were associated with the worst outcome were HACOR score (OR 1.33 CI 1.10–1.63 P = 0.004), ROX index (OR 0.86 CI 0.76–0.98 P = 0.025) male sex (OR 2.37 CI 1.10–5.27 P = 0.031), chronic kidney disease (OR 4.61 CI 1.25–21.11 P = 0.032) and respiratory rate prior to the onset of HFNC (OR 1.15 CI 1.05–1.27 P = 0.002). However, in the multivariate reduction model the variables that were associated with the worst outcome were the HACOR score (OR 1.43 CI 1.25–1.67 P < 0.001), the history of chronic kidney disease (OR 3.90 CI 1.24–15.19 P = 0.029), arterial hypertension (OR 2.46 CI 1.29–4.81 P = 0.007), respiratory rate prior to the onset of HFNC (OR 1.14 CI 1.05–1.23 P = 0.001) and the PaCo<sub>2</sub> taken prior to the initiation of HFNC (OR 0.93 CI 0.88–0.98 P = 0.005).



Table 3

Univariate and multivariate analysis of factors associated with the final composite outcome (requirement of orotracheal intubation or death by COVID19)

Predictors	Univariate analysis			Multivariate analysis		
	Odds Ratios	CI	p	Odds Ratios	CI	p
ROX Index	0.86	0.76–0.98	0.025	0.99	0.90–1.09	0.947
HACOR	1.33	1.10–1.63	0.004	1.43	1.25–1.67	< 0.001
Sex Male	2.37	1.10–5.27	0.031			
Age	1.03	0.99–1.06	0.108			
BMI†	1.04	0.96–1.12	0.367			
Atrial fibrillation	3.70	0.73–29.34	0.151			
CKD	4.61	1.25–21.11	0.032	3.90	1.24–15.19	0.029
Hypertension	2.01	0.97–4.25	0.063	2.46	1.29–4.81	0.007
COPD	0.37	0.13–0.98	0.047			
pH before HFNC	11.00	0.00–70685.37	0.589			
PaO2 before HFNC	1.01	1.00–1.03	0.183			
PaCO2 before HFNC	0.95	0.88–1.02	0.173	0.93	0.88–0.98	0.005
PaO2/Fio2 before HFNC	1.00	0.99–1.01	0.750			
Heart rate	1.01	0.99–1.04	0.301			
Respiratory rate	1.15	1.05–1.27	0.002	1.14	1.05–1.23	0.001
Glasgow coma Score	0.63	0.30–1.17	0.175			
Observations	230			230		
R <sup>2</sup> Tjur	0.344			0.285		
<p>* There were no significant differences (<math>p &lt; 0.05</math>) between the study groups. BMI denotes Body mass index, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease. HFNC High-flow nasal cannula, SaO2 blood-oxygen saturation, PaO2 Arterial partial pressure of oxygen, PaCO2 Partial pressure of carbon dioxide, Fio2 fraction of inspired oxygen.</p> <p>† the body-mass index is the weight in kilograms divided by the square of the height in meters.</p>						

In the univariate and multivariate analysis, the HACOR scale was the only one that maintained statistical significance. However, when the discrimination capacity of the HACOR and ROX scales was evaluated (Fig. 1), it was found that the AUC was similar for the two scales without significant differences (ROX AUROC 0.72 vs HACOR AUROC 0.71).

Finally, an estimate of the best cut-off point was made using the Liu method to predict the failure of the HFNC, finding that the value for HACOR scale was 5.5 with a sensitivity of 66% and a specificity of 65% (AUC for the cut-off point of 0.66) while the cut-off point for ROX scale was 5.625 with a sensitivity of 62% and a specificity of 65% (AUC for the cut-off point of 0.64).

## Discussion

In this study, we investigated the discrimination capacity of the ROX index and the HACOR scale to predict high-flow nasal cannula failure in patients with COVID19 pneumonia. Our data suggest that the discrimination capacity of the 2 scales is similar despite the scales evaluating different variables.

In our study we found that 140 (57,14%) patients required OTI and 152 (62.04%) had the final composite outcome of HFNC failure (requirement of orotracheal intubation or death by COVID19). We believe that the differences in study populations may lead to variation in findings. Compared to the report by Roca et al., our sample analyzed had a higher median age (64 vs 53 years). Also, a higher proportion of our patients on HFNC failure had CKD (13.8% vs 4.5%). Secondly, our study found that patients with atrial fibrillation had a worse outcome. This variable was not evaluated by Roca et al. Furthermore, a later study did find that a heart rate greater than 90 beats per minute was associated with a higher risk of failure of HFNC (19).

The discriminative capacity of both is similar (ROX AUROC 0.72 vs HACOR AUROC 0.71). The discriminative capacity of the ROX index is similar to those observed in other studies (16,17,18). As for the HACOR scale, so far, we do not know that it has been evaluated in patients with COVID19 infection. In our study, the discriminative capacity of the HACOR scale was similar to that reported by Innocenti et al (AUROC of 0.68). (20) but it was lower than that found by Duan et al, (AUROC of 0.89) (9) and Carrillo et al (AUROC of 0.88) (11). We believe that these differences occurred because in the studies by Duan et al, and Carrillo et al. Patients with respiratory failure secondary to causes other than COVID19 infection, as well as patients with hypercapnic respiratory failure, were taken. These findings may also be associated because in our study the discriminative capacity of the HACOR scale was taken based on a composite result of the need for orotracheal intubation and death, similar to the study by Innocenti et al. but different from the Duan study where only the need for orotracheal intubation was taken as a result. However, more studies are needed to carefully evaluate these hypotheses.

In our study, the best cut-off point for the ROX index to determine the success of HFNC was 5.62 (sensitivity 62% specificity 65%) and not 4.88, as previously established by Roca et al. (10). On the other hand, the highest cut-off point of the HACOR scale to define the success of the HFNC was 5.5 (sensitivity 66%, specificity 65%), similar to that previously reported in the literature (16,17,18,20).

Interestingly, the HACOR scale was statistically significant in the multivariate analysis when comparing variables that are not included in the calculation of this scale, unlike the ROX index, which did not achieve statistical significance. We believe that this finding is due to the fact that the HACOR scale uses a greater number of variables that reached statistical significance such as the Glasgow scale and that are not part of the ROX index. However, the discrimination capacity of the HACOR and ROX scales is similar. Given that the outcome we seek to avoid is mortality, we suggest using both scales to define the failure of the HFNC, which would provide greater safety for the patient, although this would imply a closer monitoring of the person.

Although the predictive capacity of both scales is adequate, we believe that it was not so high that it could be used as the sole criterion to predict failure of the HFNC. Therefore, we consider it necessary to add to these tools clinical variables that were also associated with the outcome of interest, such as a history of atrial fibrillation, hypertension, and chronic kidney disease. These variables could lead to the development of new models that allow a better prediction of the failure of the HFNC. New studies will be necessary to propose and evaluate these models.

Within the strengths of the study, this is the first study to compare the ability to predict cannula failure of the ROX and HACOR scales. Furthermore, it is one of the individual studies with the largest number of patients evaluated with HFNC and is the first to describe the discriminative capacity of the HACOR scale in patients with COVID19 pneumonia. Finally, we did not have data loss and we were able to count the outcomes of all the patients. Among the limitations of the study is the fact that the criteria to define the OTI requirement depended directly on the treating physician. However, the criteria for therapeutic failure to HFNC are clearly defined in our institution and these are part of a management protocol, which is why we believe that the decision for mechanical ventilation is similar among medical personnel.

## Conclusion

The HACOR scale and the ROX index have a moderate predictive capacity to predict failures to the HFNC strategy. They can be used in conjunction with other clinical variables to define which patients may require invasive mechanical ventilation.

## Declarations

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The authors declare that there is no conflict of interest regarding the publication of this article. This work was not supported by any funding.

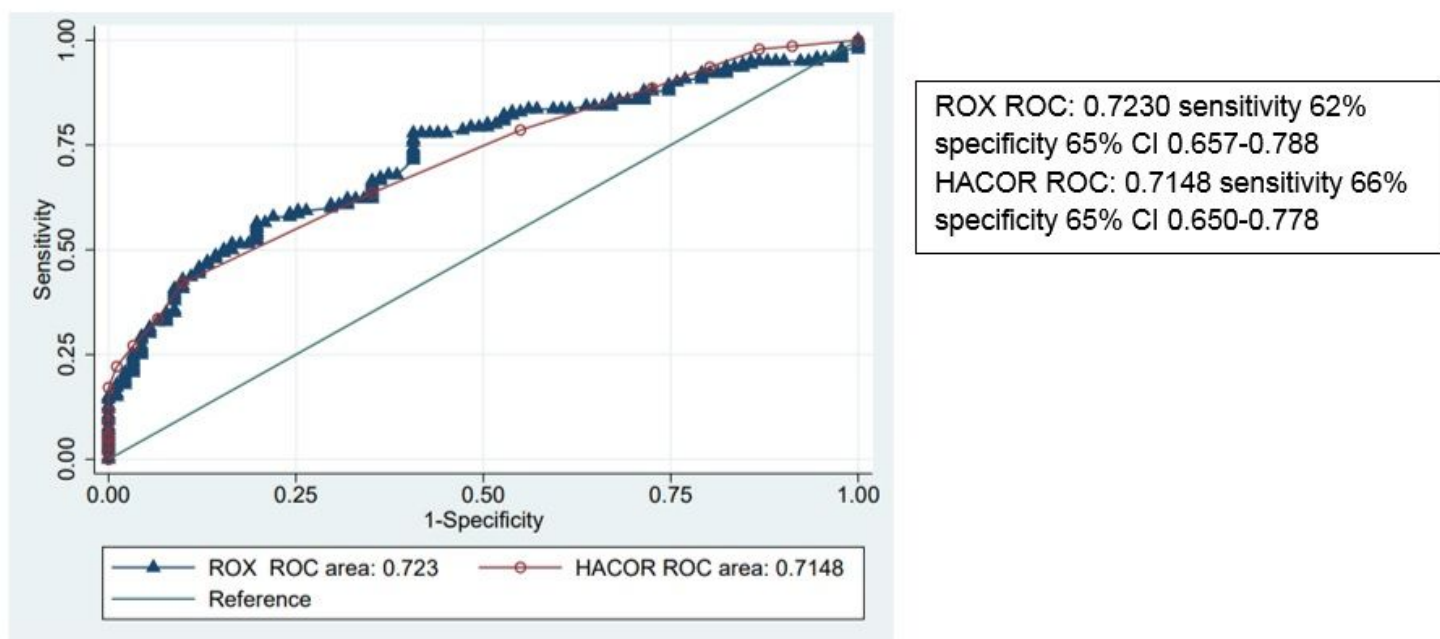
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## Figures



**Figure 1**

AUROC for HACOR and ROX scores in predicting the final composite outcome (requirement of orotracheal intubation or death by COVID19) after 2 hours of High flow nasal cannula.