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Validity ROX index in correlation with Brixia score in prediction of risk of intubation inCOVID-19 Pneumonia

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ABSTRACT

Background: A higher mortality rate is related to the risk of delayed intubation. Consequently, it is essential to evaluate the timing of intubation to identify which patients would benefit from a non-invasive oxygenation strategy.

Aim: The purpose of the research was to assess the validity of objective measures that may help clinicians to predict optimal timing for intubation in cases with covid pneumonia to avoid delayed intubation with associated morbidity and mortality.

Patients and Methods: Measuring validity of ROX index and Brixia radiological score in prediction of intubation incases diagnosed as having covid-19 pneumonia & required high flow oxygen / noninvasive mechanical ventilation or high flow nasal cannula.

Results: ROC curve of ROX mean index as predictive tool in prediction of intubation revealed the following data: AUC 0.905, P value < 0.001, Cut off point 4.35, sensitivity 70%, specificity 95%, PPV 95%, NPV 69% & accuracy 80.7%. Accordingly, ROX mean index is reliable predictive objective tool beside clinical judgement in prediction of intubation in cases with hypoxic respiratory failure 2ry to coronavirus disease pneumonia. ROC curve of BRIXIA radiological score as predictive tool in prediction of intubation revealed the following data: AUC 0.876, P value <0.001, Cut off point 12.5, sensitivity 83%, specificity 76.6%, PPV 83%, NPV 76% & accuracy 80.7%.ROC curve of ROX mean index in combination of BRIXIA radiological score as predictive tool in prediction of intubation revealed the following data: AUC 0.952, P value <0.001, sensitivity 86.6%, specificity 89.4%, PPV 92.06%, NPV 82.85% & accuracy 87.72%. Accordingly, combination of ROX index with Brixia score revealed higher sensitivity and accuracy.

Conclusion: ROX indices and BRIXIA radiological score are valid reliable simple noninvasive promising tools for expecting the risk of requiring intubation in cases with coronavirus disorder pneumonia. on high oxygen requirements and could be usable by clinicians in detecting optimal intubation timing in those patients. Further studies would be preferable to support our results.
Key Words: Validity ROX index; Brixia score; intubation; COVID-19; Pneumonia.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led in the existing coronavirus disease 2019 (COVID-19) pandemic, as provided by the World Health Organization in March 2020. This has led to significant rates of mortality &morbidity worldwide. **(1)** The clinical presentation & progression of coronavirus disease 2019 can range from no symptoms or mild symptoms in up to eighty percent of infected patients to severe viral pneumonia with acute respiratory distress syndrome (ARDS), which may require the usage of mechanical ventilatory support in the intensive care unit (ICU). **(2)** Clinicians have the problem of identifying hypoxemic COVID-19 cases who are most likely to suffer worsening respiratory function, to determine the optimum timing for intubation & starting of mechanical ventilation. This is important to avoid intubating cases who could have had positive outcomes with noninvasive ventilation. Our findings indicate that as the weeks progressed by throughout the COVID-19 crises, there was a higher frequency of delayed intubation occurring later from the time of admission. It is possible that this trend emerged because of the high mortality rates in intubated cases, causing clinicians to establish a higher threshold for intubation as time progressed, with the hope of avoiding mechanical ventilation if possible. **(3)** Delayed intubation is related to an increased mortality rate. Hence, it is essential to consider the timing of intubation to identify patients who would gain benefits from a non-invasive approach to oxygenation **(4)**. Currently, there is a absence of objective criteria for determining intubation, especially in the initial hours following the implementation of the oxygenation strategy. Recent research has evaluated many indices, involving clinical & respiratory data **(5)**, including the ROX index. The ROX index includes fraction of inspired oxygen (FiO_2), oxygen saturation (SpO_2), & respiratory rate (RR), and it is easy to use **(6)**.

The objective of the research was to assess the validity of objective measures thatmayhelpclinicianstopredictoptimaltimingforintubationinpatientwithcovidpneumoniato avoid delayed intubation withassociatedmortality andmorbidity.

Patient and methods

The ROX index and Brixia score are two clinical tools that have been proposed as predictors of the need for intubation in cases with coronavirus disease 2019 pneumonia. To assess the validity of the combination of these two tools in predicting intubation in COVID-19 pneumonia, the following methodology has been used:

<u>Study Design:</u>

A prospective cohort investigation was performed on 114 cases admitted to the critical care department of Cairo University hospitals. These cases had hypoxic respiratory failure secondary to coronavirus disease 2019 pneumonia & required high flow oxygen via non-invasive ventilation or high flow nasal cannula. The purpose of the research was to determine the validity of the ROX index in association with the Brixia score in expecting the risk of intubation in COVID-19 pneumonia.

<u>Participant Selection:</u>

Patients diagnosed as having covid-19 pneumonia by PCR & required high flow oxygen or High flow nasal cannula or noninvasive mechanical ventilation. Participants were selected depending on the following inclusion and exclusion criteria.

<u>- Inclusion criteria:</u>

- Adults > 18 years.
- Gender: Both sex eligible for study.
- SARS-COV-2: positive.
- All cases were diagnosed with covid pneumonianeeding high flow oxygen or High flow nasal cannula or noninvasive mechanical ventilation.

<u>- Exclusion criteria:</u>

- Patients less than eighteen years.
- Cases with sign for immediate intubation.
- Cases electively intubated for therapeutic or diagnostic procedures.
- History of chronic chest disease on oxygen therapy or BIPAP.

<u>Data Collection:</u>

Demographic, clinical, & laboratory data had been gathered from each participant, along with ROX index and Brixia score measurements at time of application of high flow oxygen / HFNC / NIV, and at subsequent time points if possible. Outcome data, including the need for intubation, was also collected.

<u>Ethical Considerations:</u>

Ethical clearance obtained from ethical committee Cairo university's faculty of medicine before conducting the study. Informed consent should be obtained from each participant or their legally authorized representative.

<u>Methodology in details:</u>

All patients who have covid pneumonia are confirmed by Covid-19 PCR and require high flow oxygen or High flow nasal cannula or noninvasive mechanical ventilation. All cases received standard care & therapeutic management.

ROX index:

Roca et al. devised the respiratory rate oxygenation index to predict the requirement of mechanical ventilation &intubation in cases who received HFNO because of acute respiratory failure 2ry to bacterial pneumonia. The respiratory rate oxygenation index, which is described as the ratio of oxygen saturation /fraction of inspired oxygen to the RR, is readily measurable at the patient's bedside. **(6)**

We calculated ROX index at 2,4,6,12,24,48 Hours after application of high flow oxygen or High flow nasal cannula or noninvasive mechanical ventilation. The respiratory rate oxygenation index, described as the ratio of oxygen saturation as determined by pulse oximetry/fraction of inspired oxygen to respiratory rate. In those cases who required application of high flow oxygen / HFNC / NIV more than 48 hours or increasing percentage of FIO2 or required intubation later we included ROX index at highest FIO2 applied for 48 hours or 48 hours prior to intubation as ROX index is variable index and it's prediction ability varies with variation of included parameters. Also, to be noted, we were calculating ROX index during whole duration of application of high flow oxygen / HFNC / NIV.

Brixia score:

The Brixia radiological score is a recently developed scoring system used to assess the severity of coronavirus disease 2019 pneumonia on chest X-rays. It was developed by a team of Italian radiologists in response to the urgent need for a reliable and standardized method of assessing the severity of coronavirus disease 2019 pneumonia. The Brixia score consists of six categories, each assigned a score varying from zero to three, depending on the severity of lung involvement. The categories include the degree of lung involvement, the presence of consolidation or ground-glass opacities, the presence of pleural effusion, and the degree of lung involvement in each lung. The overall score varies from zero to eighteen with greater scores representing a more extent of illness severity.**(7)**

We determined the Brixia score at the time of administering high flow nasal cannula, high flow oxygen, or noninvasive mechanical ventilation. The CXR scoring system, often known as the Brixia score, for coronavirus disease 2019 pneumonia involves two stages of image analysis.

In the 1st step, the lungs are separated into 6areas on frontal chest projection (anteroposterior or posteroanterior projection corresponding to the case position):

- Upper zones: It's superior to the inferior wall of the aortic arch.
- Middle zones: It's above the inferior wall of the right inferior pulmonary vein &beneath the inferior wall of the aortic arch. (i.e., the hilar structures).
- Lower zones: that is beneath the inferior wall of the right inferior pulmonary vein (i.e., the lung bases).

For technical reasons (such as bedside CXR in critical cases), Identifying certain anatomical landmarks may provide difficulties. It is advisable to divide each lung into 3identicalareas in such cases.

In the 2nd step, a score (from zero to three) A zone is assigned to each area depending on the lung disorder identified on the frontal chest projection, according to the following criteria:

- Score zero that there are no lung abnormalities.
- Score oneindicates interstitial infiltrates.
- Score twoindicates alveolar &interstitial infiltrates (interstitial predominance).
- Score threealveolar &interstitial infiltrates (alveolar predominance).

The scores of the 6 lung areas are then added to obtain an whole “CXR SCORE” varying from zero to eighteen.

For assessment of covid severity we used Covid-19 critical illness prediction tool (COVID-GRAM) which include the following variables: Age, Unconsciousness, Dyspnea, Hemoptysis, Cancer history, Number of comorbidities, CXR abnormality, Neutrophil/lymphocyte ratio, LDH & Direct bilirubin. **(8)**

In addition, for all patient included in this study we estimated SOFA score, APACHE II score at time of estimation of ROX 0 & we included the following laboratory measures: C-reactive protein, Procalcitonin, Troponin, Ferritin, D-dimer, Lactate dehydrogenase. **(9,10)**

Outcomes:

The primary purpose of this research was to evaluate the validity of the respiratory rate-oxygenation index and Brixia score in predicting the risk of intubation in hypoxemic respiratory failure secondary to COVID-19 pneumonia, as well as the impact of their combination on prediction validity.

The secondary outcomes of our research to detect risk factors associated with severity of covid pneumonia & correlation of intubation with other parameters & correlation of ROX index with other parameters & predictors or risk factors relatedto prolonged ICU stay or mortality in covid-19 pneumonia.

The validity of the combination of respiratory rate-oxygenation index and Brixia score in predicting intubation had been assessed using appropriate statistical methods. The specificity, negative predictive value, sensitivity, &positive predictive value of the combination had been calculated, as well as the area under the receiver operating characteristiccurve. The optimal cutoff values for the respiratory rate-oxygenation index & Brixia score had also been determined.

Results

Table (1): Demographic, clinical, different scores & laboratory data of cases with confirmed COVID-19

	Mean	Standard Deviation	Median	Minimum	Maximum
AGE	65.67	12.47	65.50	23.00	90.00
BMI	33.26	7.69	33.50	18.00	52.00
SO2 Ad.	85.70	12.64	90.00	44.00	98.00
ROX0	4.79	1.70	4.45	2.00	11.10
ROX2	4.96	2.03	4.45	1.80	13.80
ROX4	5.18	2.13	4.95	1.90	13.60
ROX6	5.38	2.14	4.90	2.20	11.80
ROX12	5.57	2.27	5.15	2.40	12.80
ROX24	5.65	2.91	4.80	2.00	17.50
ROX48	5.81	3.22	5.00	2.14	17.90
ROX MEAN	5.01	1.96	4.80	2.00	12.10
ROX INTUBATION	2.96	0.55	2.90	1.90	4.80
BRIXIA	12.43	2.90	13.00	5.00	17.00
GRAM	176.60	33.91	177.00	108.00	308.00
SOFA	4.59	1.44	4.00	3.00	9.00
APACHEII	12.70	5.08	12.00	3.00	28.00
CRP	146.89	87.61	139.50	18.00	515.00
PCT	1.45	4.06	0.18	0.01	32.00
TROPONINE	140.56	407.73	14.20	0.50	3220.00
DIMER	3.98	6.99	1.03	0.20	35.00
FERRITIN	1210.11	1403.44	725.00	46.00	9987.00
LDH	542.64	230.26	485.00	230.00	1500.00
ICU STAY	16.38	18.11	13.00	1.00	140.00

This table shows that mean of age was 65.67±12.47, mean of BMI was 33.26±7.69, mean of SO2 Ad. was 85.70±12.64, mean of ROX0 was 4.79±1.70, mean of ROX2 was 4.96±2.03, mean of ROX4 was 5.18±2.13, mean of ROX6 was 5.38±2.14, mean of ROX12 was 5.57±2.27, mean of ROX24 was 5.65±2.91, mean of ROX48 was 5.81±3.22, mean of ROX MEAN was 5.01±1.96, mean of ROX INTUBATION was 2.96±0.55, mean of BRIXIA was 12.43±2.90, mean of GRAM was 176.60±33.91, mean of SOFA was 4.59±1.44, mean of APACHEII was 12.70±5.08, mean of CRP was 146.89±87.61, mean of PCT was 1.45±4.06, mean of TROPONINE was 140.56±407.73, mean of DIMER was 3.98±6.99, mean of FERRITIN was 1210.11±1403.44, mean of LDH was 542.64±230.26 and mean of ICU STAY was 16.38±18.1.

Table (2): Distribution of patients with confirmed COVID-19 as regards different parameters.

		Count	%
SO2 Ad.	**<80**	26	22.8%
	80-90	33	28.9%
	>=90	55	48.2%
BRIXIA	**<9**	17	14.9%
	>=9	97	85.1%
COVID severity	**moderate**	12	10.5%
	severe	102	89.5%

intubation	**Yes**	67	58.8%
	No	47	41.2%
intubation day	**Day 1**	31	46.3%
	Day 2-3	25	37.3%
	Day 4 or more	11	16.4%
ICU STAY	**1 week**	42	36.8%
	2-3 weeks	20	17.5%
	>2 weeks	52	45.6%
mortality	**yes**	52	45.6%
	no	62	54.4%

This table shows that 22.8% had SO2 Ad. <80, 28.9% had SO2 Ad. Ranging from 80-90%, 48.2% had SO2 Ad. >90%, 14.9% had BRIXA score < 9, 85.1% had BRIXA score > 9, 10.5% had moderate COVID-19, 89.5% had severe COVID-19, 58.8% were intubated, 41.2% were not intubated, 46.3% were intubated on 1st day , 37.3% were intubated on 2nd – 3rd days , 16.4% were intubated on 4th day or after , 36.8% had ICU stay up to 1 week , 17.5% had ICU stay ranging from 1 to 2 weeks , 45.6% had ICU stay more than 2 weeks , 45.6 % died and 54.4% survived.

Table (3): Relation of intubation with different parameters among patients with confirmed COVID-19

		intubation				
		Yes		**No**		**P value**
		Count	**Row N %**	**Count**	**Row N %**	
Sex	**M**	45	73.8%	16	26.2%	< 0.001
	F	22	41.5%	31	58.5%	
BMI	**<25**	7	46.7%	8	53.3%	0.250
	25-30	14	51.9%	13	48.1%	
	30-35	22	73.3%	8	26.7%	
	>35	24	57.1%	18	42.9%	
DM	**yes**	53	60.9%	34	39.1%	0.403
	no	14	51.9%	13	48.1%	
HTN	**yes**	52	59.8%	35	40.2%	0.698
	no	15	55.6%	12	44.4%	
CVS	**yes**	19	50.0%	19	50.0%	0.178
	no	48	63.2%	28	36.8%	
CKD	**yes**	17	68.0%	8	32.0%	0.289
	no	50	56.2%	39	43.8%	
CLD	**yes**	2	66.7%	1	33.3%	1
	no	65	58.6%	46	41.4%	
CNS	**yes**	10	66.7%	5	33.3%	0.505
	no	57	57.6%	42	42.4%	
immunodeficiency	**yes**	7	58.3%	5	41.7%	1
	no	60	58.8%	42	41.2%	
SO2 Ad.	**<80**	23	88.5%	3	11.5%	0.002
	80-90	17	51.5%	16	48.5%	
	>=90	27	49.1%	28	50.9%	
BRIXIA	**<9**	1	5.9%	16	94.1%	< 0.001

	>=9	66	68.0%	31	32.0%	
COVID severity	moderate	5	41.7%	7	58.3%	0.228
	severe	62	60.8%	40	39.2%	

There was significant correlation between intubation and male gender as 73.8% of male cases with covid pneumonia were intubated (P <0.001).

Table (4): Association of mean respiratory rate-oxygenation with other parameters

	ROX MEAN		
	Correlation Coefficient	**P value**	**N**
AGE	-0.146-	0.121	114
BMI	-0.048-	0.615	114
SO2 Ad.	0.215	0.021	114
BRIXIA	-0.492-	< 0.001	114
GRAM	-0.186-	0.047	114
SOFA	-0.200-	0.033	114
APACHEII	-0.371-	< 0.001	114
CRP	-0.169-	0.072	114
PCT	-0.200-	0.033	114
TROPONINE	-0.092-	0.329	114
DIMER	-0.145-	0.123	114
FERRITIN	-0.094-	0.319	114
LDH	-0.207-	0.027	114
ICU STAY	-0.478-	< 0.001	114

This table shows that there was significant positive relationship between ROX mean and SO2 Ad. with significant P value 0.021, while there was significant inverse relationship among ROX mean and the following parameters: BRIXIA score, GRAM score, sequential organ failure assessment score, APACHE II score, LDH &intensive care unit stay with significant P values (<0.001 & 0.047& 0.033 &<0.001 & 0.033 & 0.027 &<0.001 respectively).

Table (5): Multivariate logistic regression for prediction of intubation

		B	**P value**	**OR**	**95% C.I.**	
					Lower	**Upper**
Intubation	**ROX MEAN**	-1.847-	< 0.001	0.158	0.062	0.399
	BRIXIA	0.808	< 0.001	2.243	1.447	3.476
	APACHEII	0.198	0.031	1.219	1.018	1.459
	FERRITIN	0.001	0.018	1.001	1.000	1.001
	Constant	-3.503-	0.304	0.030		

Classification Table

			Predicted		
			Intubation		**Percentage Correct**
	Observed		**No**	**Yes**	
Observed	**intubation**	**No**	40	7	85.1
		Yes	3	64	95.5
	Overall Percentage				91.2

	Chi-square	**P value**
Model	105.712	< 0.001

Variables entered in the model: Age, Sex, SO2 Ad., and BRIXIA score, mean ROX, SOFA score, APACHE II score, CRP, PCT, TROPONINE, FERRITIN, LDH.
This table shows that the following parameters: ROX MEAN index, BRIXIA score, APACHE II score and Ferritin level were independent predictors for intubation in COVID-19 cases with significant P values (< 0.001 &< 0.001 & 0.031 & 0.018 respectively). Percent correctly predicted =91.2%

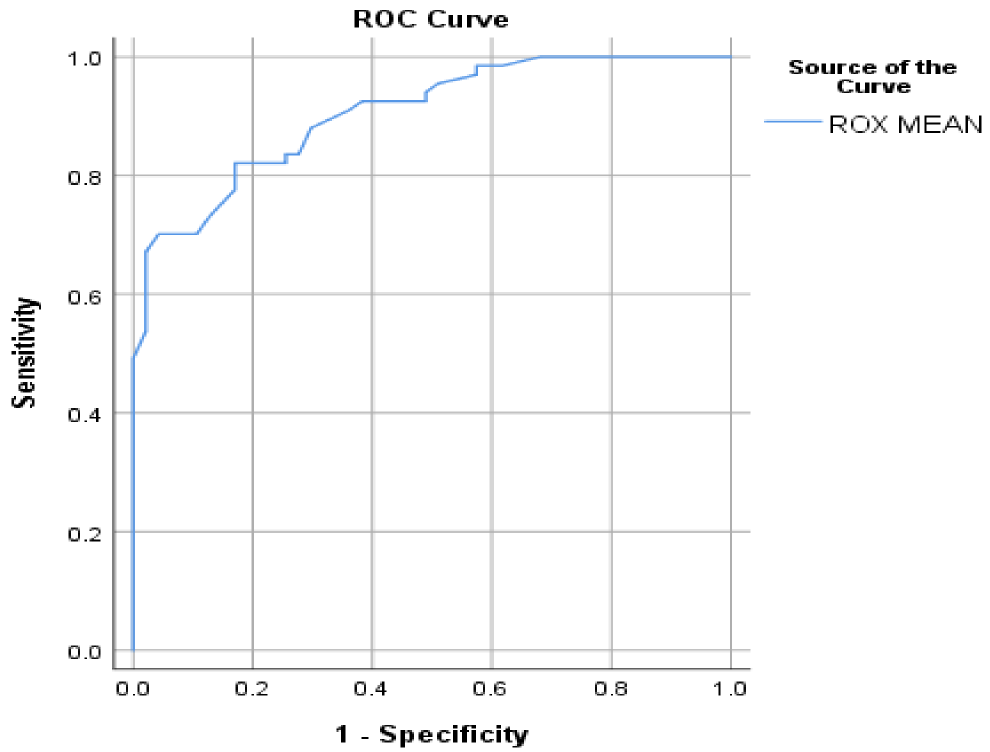

Figure1: ROC curve for prediction of intubation using ROX mean index.

ROC curve of ROX mean index as predictive tool in prediction of intubation revealed the following data: AUC 0.905, P value <0.001, Cut off point 4.35, sensitivity 70%, specificity 95%, PPV 95%, NPV 69% & accuracy 80.7%. Accordingly, ROX mean index is reliable predictive objective tool beside clinical judgement in expectation of intubation in cases with hypoxic respiratory failure 2ry to coronavirus disease pneumonia.

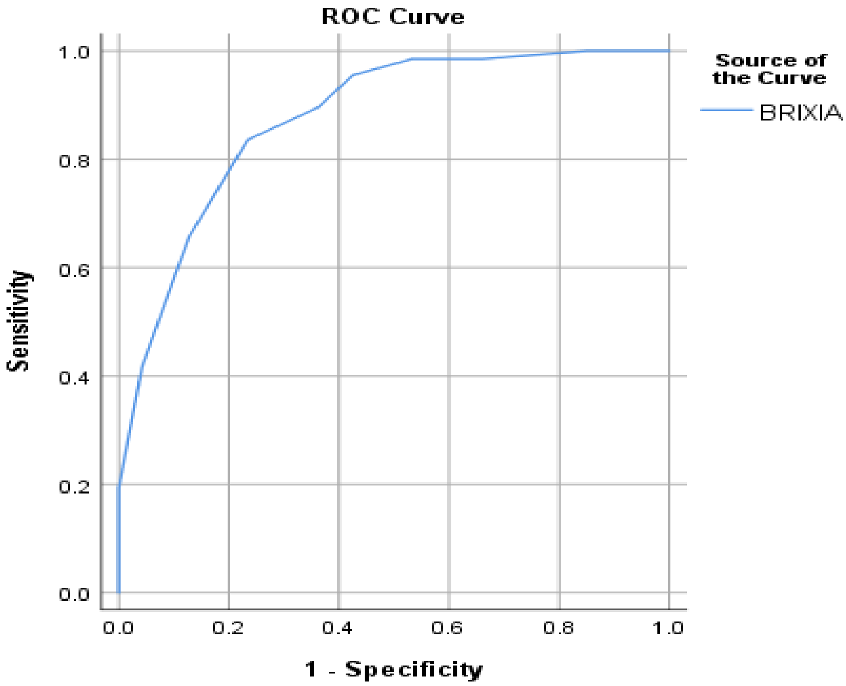

Figure 2: ROC curve for prediction of intubation using BRIXIA score.

ROC curve of BRIXIA radiological score as predictive tool in prediction of intubation revealed the following data: AUC 0.876, P value <0.001, Cut off point 12.5, sensitivity 83%, specificity 76.6%, PPV 83%, NPV 76% & accuracy 80.7%.
Accordingly, BRIXIA radiological score is reliable predictive objective tool (with lesser sensitivity, more specificity and same accuracy than ROX index) beside clinical judgement in prediction of intubation in cases with hypoxic respiratory failure secondary to coronavirus disease pneumonia.

ROC curve of ROX mean index in combination of BRIXIA radiological score as predictive tool in prediction of intubation revealed the following data: AUC 0.952, P value <0.001, sensitivity 86.6%, specificity 89.4%, PPV 92.06%, NPV 82.85% & accuracy 87.72%. Accordingly, ROX mean index in combination of BRIXIA radiological score (with more sensitivity & accuracy and lesser specificity than ROX index alone) is reliable predictive objective tool beside clinical judgement in prediction of intubation in cases with hypoxic respiratory failure secondary to coronavirus disease pneumonia.

Discussion

The coronavirus pandemic is currently recognized as one of the most lethal epidemics, causing major damage to global health and financial systems.**(11)**.
The objective of the research is to assess the validity of objective measures that may help clinicians to predict optimal timing for intubation in cases with covid pneumonia to avoid delayed intubation with associated morbidity and mortality.
In our research , There was significant correlation among intubation and following parameters: male gender (73.8% of male patients with covid pneumonia were intubated - P value < 0.001) & age (mean age of intubated cases was 67.9±10.52 - P value 0.01) & oxygen saturation of admission (88.5% 0f patient presented with SO2 less than 80% were intubated -

P value 0.002) & ROX mean (mean of ROX mean of intubated patients was 3.97±1.04 - P value < 0.001) & BRIXIA score (94.1% of patients had score less than 9 were not intubated & 68% of patients had score equal or more than 9 were intubated - P value < 0.001) (mean of BRIXIA score of intubated cases was 14.01±1.86 - P value < 0.001) & SOFA score (mean of SOFA score of intubated patients was 4.87±1.44 - P value 0.003) & APACHIE II score (mean of APACHIE II score of intubated cases was 14.36±5.02 - P value < 0.001) & CRP (mean of CRP of intubated cases was 164.63±93.8 - P value < 0.014) & PCT (mean of PCT of intubated patients was 2.16±5.14 - P value 0.002) & Troponin (mean of Troponin of intubated patients was 178.56±463.69 with P value 0.007) & Ferritin (mean of Ferritin of intubated cases was 1372.82±1278.34 with P value 0.025) & LDH (mean of LDH of intubated patients was 607.09±262.69 with P value < 0.001).

Hur et al. (2020) (12) investigated on hospitalized cases with COVID-19 and discovered that intubated cases had a greater median age (sixty-fiveversus fifty seven years, P < .001), a greater percentage of males (63.8% versus 52.6 percent, P value = .033), & more prevalent of diabetes (40.6 percent versus 29.9 percent, P value= .031). Intubated cases were also more likely to suffer from shortness of breath (84.1% versus 65.2 percent, P value< .001), have a respiratory rate greater than 24/min (31.9% versus 12.9%, P < .001), a temperature higher than 100.4 °F (39.9% versus 28.4 percent, P value= .033), & a lower oxygen saturation level .(001. >)

Furthermore, the research conducted by **Kim et al. in 2022 (13)** examined the utilize of the SpO2/FiO2 ratio &ROX index as predictors of high-flow nasal cannula failure in hypoxemic coronavirus disease 2019 cases. The research indicated that the group of cases who require intubation consisted of older cases with higher SOFA scores & APACHE II scores compared to the group who did not require intubation.

In line with our findings, an investigation conducted by **Suliman et al. in 2021 (14)** investigated the accuracy of the ROX index in predicting the risk of intubation in cases with COVID-19 pneumonia. They discovered a significant association between the ROX one, two, and three indices and the risk of intubation (p < 0.001 for each index). The categorizing of coronavirus disease 2019 based on clinical criteria showed a significant correlation with the need for intubation (p < 0.001). Every case with a severe case of COVID-19 (100%) required intubation.

The study of **Rodriguez et al. 2019(15)** about Predictors of successful separation from high-flow nasal oxygen treatment in cases with acute respiratory failure reported that FiO2 ≤ 40% was revealed to be a good predictor of HFNC weaning with a sensitivity reaching eighty five percent& specificity of forty one percent, so it is recommended to wean from HFNC starting from FiO2 ≤ 40%. In addition, the increased level of PaCO2 indicated respiratory muscles fatigue due to the inspiratory workload, which lead to respiratory failure and poor outcomes.

Supporting our results, **Claudi et al. 2022 (16)** study about the role of respiratory rate-oxygenation index in predicting intubation in coronavirus disease 2019 pneumonia receiving high flow nasal cannula also showed there was a significant rise in D-dimer levels and was concluded as a good predictor for HFNC failure and intubation. Also, he found that patients who had severe COVID-19, comorbidities, and age > 60 years old were significantly correlated with the lower value of ROX index and intubation (p ≤ 0.005).

In our study, there was significant positive relationship between ROX mean and SO2 on Admission with significant P value 0.021, while there was significant inverse connectionamong ROX mean and the following parameters: BRIXIA score, COVID-GRAM score, sequential organ failure assessment score, APACHE II score, LDH &intensive care unit stay with significant P values (< 0.001 & 0.047& 0.033 &< 0.001 & 0.033 & 0.027 &< 0.001 respectively).

Like our results, **Suliman et al. 2021(14)** found that ROX.1 was significantly Correlated with the SpO2 ($p \leq 0.001$). Also, there was a negative significant correlation with LDH & BRIXA ($p = 0.022$, $r = -0.276$).

Nguyen et al. (2021) (17) investigated coronavirus disease 2019 pneumonia patients with acute respiratory failure, focusing on the admission respiratory rate-oxygenation (ROX) index and its connection with outcome. The researchdiscovered a significant positive association among the admission ROX index and SO2 ($r = 0.28$; $p = 0.01$), & a negative association with the BRIXIA score ($r = -0.027$, $p = 0.04$).

In our study we illustrated that ROX MEAN index, BRIXIA score, APACHE II score and Ferritin level were independent predictors for intubation in COVID-19 cases with significant P values (< 0.001 &< 0.001 & 0.031 & 0.018 respectively).

Consistent with our findings, the research conducted by **Fayed et al. in 2021 (18)** on the impact of intubation timing on the outcomes of cases with severe respiratory distress caused by coronavirus disease 2019 pneumonia revealed that the early intubation group (intubated within twenty-four hours of the start of severe respiratory distress) had a significantly greater percentage of cases with a decreased risk of intubation (45%) compared to the late group (intubated following twenty-four hours of the beginning of severe respiratory distress) (twenty-seven percent) ($p = 0.029$), as determined by the ROX index .

Furthermore, **Kim et al. (2022) (13)** discovered that the univariate analysis demonstrated a significant association between intubation & many factors including age, CURB-65, sequential organ failure assessment score, CURB-65, hypertension, APACHE II score, 1 h SpO2/FiO2 ratio, 4 h SpO2/FiO2 ratio, 1 h respiratory rate-oxygenation index, & 4 h respiratory rate-oxygenation index.

In accordance with our findings, the research conducted by **Patel et al. in 2020 (19,20)** on the value of the respiratory rate-oxygenation Index in predicting intubation for cases with coronavirus disease 2019-related hypoxemic respiratory failure receiving high-flow nasal treatment discovered that ΔROX, peak D-dimer levels exceeding 4000, and BRIXIA score upon admission were highly indicative of the requirement for invasive mechanical ventilation (ROC = 0.86, p=<0.001).

In an investigation conducted by **Balbi et al. in 2020, (21)** it was found that certain factors can predict the need for ventilatory support in coronavirus disease 2019 cases that arrive to the emergency department. These factors include the Brixia score, age, SpO2 levels, and Ferritin levels. The research showed that the Brixia score, age, SpO2 levels, and Ferritin levels were significantly associated with the need for ventilation.

In accordance with our findings, **Rodriguez et al. (2019) (15)** discovered that the ROX index in critically sick cases in the intensive care unit was greater in cases who were able to effectively discontinue high-flow nasal cannula during the initial attempt compared to those who were failed (12.7 versus 10.2, p value= 0.002).

The findings of our investigation are consistent with those of **Mueller et al. 2020 (22)**, who determined that the level of Ferritin and the change in Ferritin from day zero to day one (Δ Ferritin), as well as the ROX index, significantly indicate the need for advanced respiratory assistance in coronavirus disease 2019 cases.

In our study, the following parameters are significant risk factors for mortality in COVID-19 cases: Sex (male gender) (60.7% of male patients died - P value 0.001) & Oxygen Saturation on admission (SO2 Ad.) (73.1% of patients presented with Oxygen Saturation on admission less than 80% died - P value 0.006) & Covid severity is considered as significant risk factor of mortality as 83.3% of patients presented with moderate covid pneumonia survived (P value 0.033) & ROX MEAN index (cases with ROX MEAN 3.99±1.04 died - P value <0.001) & BRIXIA score (100% of cases presented with BRIXIA score less than 9 survived - P value < 0.001) (c with asesBRIXIA score 14.21±1.53 died - P value <0.001) & SOFA score (cases with SOFA score 5.02±1.50 died - P value 0.001) & APACHE II score (cases with APACHE II score 14.81±5.12 died - P value < 0.001) & PCT (cases with PCT 2.42±5.68 died - P value 0.005) & Troponin (patients with troponin 218.3±519.72 died - P value 0.003) & LDH (patients with LDH 645.98±237.37 died - P value <0.001).

In accordance with our findings, **Fayed et al. 2021 (18)** discovered that patients with a SOFA score among zero and nine had a significantly greater mortality rate in the late intubation group (forty nine percent) compared to the early intubation group (twenty six percent) (p = 0.03). Cases in the zero to nine sequential organ failure assessmentgroup who were intubated later had 2.7 times higher chances of dying throughout their hospital stay compared to cases who were intubated early. The confidence interval for this finding is 1.09 to 6.67.

Balbi et al. 2020 (21) discovered that deceased cases were significantly older & had a greater number of comorbidities. Additionally, these cases had significantly reduced SpO2 values & more severe CXR findings upon admission to the emergency department compared to those who survived (p < 0.001).

Consistent with our findings, **Kim et al. 2022 (13)** discovered that, based on the results of the multivariable analysis, the risk of mortality in cases aged seventy years or more was 4.9 times greater than in those aged lower than seventy years (heart rate 4.867 [ninety five percentconfidence interval: 1.772–13.364], p = 0.002). Cases who had a Sequential Organ Failure Assessment (SOFA) score of three or above had a 4.4 times greater risk of death compared to those with a SOFA score below three (Hazard Ratio 4.437 [95% Confidence Interval: 1.770–11.120], p = 0.001).

Gianstefani et al. (2021) (23) investigated involving 554 cases who were admitted to the emergency department with severe acute respiratory syndrome coronavirus 2 infection. They discovered that the respiratory rate-oxygenation index, measured upon admission, was related to both hospitalization & mortality within a thirty-day period. It is worth noting that the cut-off points used in this research were quite high (25.7 & 22.3, respectively). Additionally, the research involved cases with mild upper respiratory tract illness as well as pneumonia.

The findings of our investigation are agreed with the research performed by **Bhorgesi et al. in 2020 (24)**. They evaluated the initial chest X-rays of 302 cases using the Brixia scoring system & determined that a high Brixia score was strongly correlated with an increased risk of mortality during hospitalization.

In a study performed by **Zucman et al. in 2020, (25)** it was found that a respiratory rate-oxygenation index of ≥ 5.37, measured approximately 4 hours after the usage of high-flow nasal cannula (HFNC) in cases with coronavirus disease 2019 -related acute hypoxemic respiratory failure, was strongly related to a reduced risk of requiring intubation. This finding suggests a low mortality rate of three percent.

The findings of our investigation are agreed with the investigationperformed by **Nassar et al. in 2021 (26)** on the outcomes & risk factors for death in cases with coronavirus disease 2019 pneumonia admitted to intensive care units. Their research concluded that ischemic heart disease, a history of smoking, & secondary bacterial pneumonia was independently related to an elevated risk of in-hospital death.

In our study, the following parameters are significant associated risk factors for prediction of ICU stay: BMI (60% of cases with BMI (30-35) and 52.4% of cases with BMI (>35) stayed in ICU more than 2 weeks while 60% of patients with BMI (<25) stayed in ICU less than 1 week) & CKD (68% of patients with CKD stayed in ICU more than 2 weeks) & ROX mean (significant inverse relationship between ROX mean and ICU stay of 1-2 weeks duration with significant P value < 0.001) & BRIXIA score (88.2% of patients with BRIXIA score less than 9 stayed in ICU less than 1 week while 52.6% of patients with BRIXIA score equal or more than 9 stayed in ICU more than 2 weeks. - P value < 0.001) & PCT (significant correlation between PCT and ICU stay of 1-2 weeks duration with significant P value 0.002).

Supporting our results, **Rodriguez et al. 2019 (15)** found that ICU length of stay was significantly longer among cases who had lower values of SpO2 and ROX index ($p < 0.001$).
In our study, ROC curve of ROX mean index as predictive tool in prediction of intubation revealed the following data: AUC 0.905, P value < 0.001, Cut off point **4.35**, sensitivity 70%, specificity 95%, PPV 95%, NPV 69% & accuracy 80.7%. Accordingly, ROX mean index is reliable predictive objective tool beside clinical judgement in prediction of intubation in cases with hypoxic respiratory failure secondary to covid pneumonia.
ROC analysis for ROX 1, 2, and 3 (ROX indices sum on first, second, and third day of admission) as predictors of intubation, as determined by **Suliman et al. 2021 (14)** revealed (area under the curve, p value): (0.897, ≤ 0.001), (0.896, ≤ 0.001), and (0.967, ≤ 0.001), respectively, like our findings. The cut-off points for respiratory rate-oxygenation.1, respiratory rate-oxygenation.2, &respiratory rate-oxygenation.3 were as follows: ≤ 25.26 (90.2 percent sensitivity & seventy-five percent specificity), ≤ 21.34 (ninety percent sensitivity and seventy-five percent specificity), & ≤ 11.71 (90% sensitivity & one hundred percent specificity).
Additionally, **Rodriguez et al. 2019 (15)** discovered that a ROX index of 9.2 or higher predicted effective separation from HFNC in the first trial (specificity of fifty percent, sensitivity of eighty-four percent, positive predictive value of ninety-three percent, negative predictive value of thirty percent, & accuracy of eighty percent). The ROX index was calculated for a period of forty-eight hours.
The research conducted by **Roca et al. 2019 (6)** revealed that a ROX index of less than 4.88 was independently correlated with a greater risk of intubation. Additionally, ROX indexes of fewer than 2.85, fewer than 3.47, and less than 3.85 at 2, 6, & twelve hours of high-flow nasal cannula initiation had specificities of 99.2 percent, 99.2 percent, and 98.4%, respectively, with AUC of 0.679, 0.703, and 0.759. The investigation conducted by Roca et al. determined that a respiratory rate-oxygenation index of 4.88 or higher at twelve hours following HFNC therapy was indicative of a high degree of success in HFNC therapy, while a ROX index of less than 3.85 indicated a high risk of HFNC failure. The gray area among 3.85 and 4.88 indicated that the respiratory rate-oxygenation index calculation should be repeated one or two hours later. If the score has risen, the case should be believed to have an elevated risk of success; similarly, if the score has declined, there is a greater risk of intubation. It should only take an hour or two to determine the ROX index if the score remains unchanged. Therefore, it was recommended that the ROX index be computed at various time intervals.
Additionally, **Belz et al. (2020)(27)** employed the original threshold value of 4.88 to forecast the necessity for intubation in intensive care cases who underwent HFNO as a result of COVID-19. They discovered eighty-one percent sensitivity and thirty-eight percent specificity.
Murat et al. (2022) (28) confirmed our findings by determining that a chest CT score of >15 (odd ratio2.83, ninety-five percent confidence interval = 1.01–7.88, P = <0.001) and a respiratory rate-oxygenation computed on the 1st hour of treatment of < 3.81 (odd ratio = 4.78, [ninety-five percent confidence interval = 1.75–13.02], P = 0.001) were independent risk factors for HFNO failure.
In the 2022 experiment conducted by **Borghesi et al. (29),** pulmonary involvement was assessed using the Brixia score for chest X-rays and the percentage of well-aerated lung (WAL) for computed tomography. The Brixia score was assigned upon admission (referred to as A-Brixia score) and continued to be assessed during the whole hospital stay. Throughout the hospitalization, only the highest score, known as the H-Brixia score, was considered. The well-aerated lung percentage (A-CT%WAL) was measured using specialized software upon admission. The H-Brixia score demonstrated the highest efficacy as a

radiological marker in predicting both in-hospital mortality & the need for invasive mechanical ventilation, as determined using logistic regression analyses. In addition, the A-CT%WAL score did not offer any notable benefits in categorizing the risk of hospitalized cases with coronavirus disease 2019 contrasted to the A-Brixia score.
In accordance with our findings, **Hanley et al. (2022) (30)** investigated on the Modified Brixia chest X-ray severity scoring system & its association with intubation, non-invasive ventilation, & death in a hospitalized coronavirus disease 2019 cohort. The research stated that the median scores of the pre-intubation intensive care unit chest X-rays were 11.5 (IQR 9-14.125), which was a rise from the median admission chest X-ray score of 9 for ICU cases admitted by COVID-19 (P-value < 0.01). The sensitivity & specificity of a cut-off score of six in predicting the necessity of intubation were 77% and 73%, respectively.
In our study, ROC curve of BRIXIA radiological score as predictive tool in prediction of intubation revealed the following data: AUC 0.876, P value < 0.001, Cut off point 12.5, sensitivity 83%, specificity 76.6%, PPV 83%, NPV 76% & accuracy 80.7%. Accordingly, BRIXIA radiological score is reliable predictive objective tool (with lesser sensitivity, more specificity than ROX index and same accuracy) beside clinical judgement in prediction of intubation in cases with hypoxic respiratory failure secondary to coronavirus disease pneumonia.
In our study, ROC curve of ROX mean index in combination of BRIXIA radiological score as predictive tool in prediction of intubation revealed the following data: AUC 0.952, P value < 0.001, sensitivity 86.6%, specificity 89.4%, PPV 92.06%, NPV 82.85% & accuracy 87.72%. Accordingly, ROX mean index in combination with BRIXIA radiological score revealed more sensitivity & accuracy and lesser specificity than ROX index alone.
Supporting our results, **Busani S. et al., 2021 (31)** concluded that the combination of the ROX index and BRIXIA score showed a sensitivity of 92.7%, specificity of 90.7%, PPV of 77.6%, NPV of 97.0%, and accuracy of 91.8% in predicting the risk of intubation. The combination of the ROX index and BRIXIA score showed better performance than the ROX index and the BRIXIA score alone in expecting the risk of intubation in coronavirus disorder 19 cases. The use of a combination of clinical & laboratory parameters may improve the accuracy of predicting the risk of intubation in COVID-nineteen cases.

Our investigation is limited by numerous constraints. First, it was performed at a single-center hospital, despite being prospective. Second, the results may be influenced by the relatively tiny sample size. One final restriction pertains to the utilization of SpO2 in the ROX index, as instead of PaO2. Nevertheless, the efficacy of SpO2/FiO2 in patients with ARDS is demonstrated by its strong correlation with PaO2/FiO2.
In conclusion, ROX indices with cutoff point 4.3 and BRIXIA radiological score with cutoff value 12 are valid reliable simple noninvasive promising tools for expecting of risk of intubation in cases with covid pneumonia on high oxygen requirements and could be usable by clinicians in detecting optimal intubation timing in those patients. Further studies would be preferable to support our results.

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