

ROX Index as a Predictor of Intubation Risk and 28-Day Mortality in COVID-19 Patients with Acute Respiratory Distress Syndrome

Putra Kurnia Nugraha¹, Arie Utariani^{2*},
Philia Setiawan³, Bambang Pujo Semedi⁴

¹Anesthesiologist; Department of Anesthesiology and Intensive Therapy; Faculty of Medicine Universitas Airlangga; Dr. Soetomo General Hospital Surabaya

²Consultant of Pediatric Anesthesia; Department of Anesthesiology and Intensive Therapy; Faculty of Medicine Universitas Airlangga; Dr. Soetomo General Hospital Surabaya

³Consultant of Cardiovascular Anesthesia & Intensive Care; Department of Anesthesiology and Intensive Therapy; Faculty of Medicine Universitas Airlangga; Dr. Soetomo General Hospital Surabaya

⁴Consultant of Intensive Care; Department of Anesthesiology and Intensive Therapy; Faculty of Medicine Universitas Airlangga; Dr. Soetomo General Hospital Surabaya

*Corresponding author details: Arie Utariani; arieturiani1955@gmail.com

ABSTRACT

Background: The main concern when treating COVID-19 acute respiratory distress syndrome (ARDS) during high flow nasal cannula (HFNC) is delayed intubation, thus increasing the risk of prior mortality. This study aims to analyze the prognostic ability of the Respiratory Rate Oxygenation (ROX) index as a predictor for intubation and 28-days mortality in COVID-19 patients.

Methods: A retrospective analysis of COVID-19 patients admitted to Intensive Care Unit (ICU) Dr. Soetomo General Hospital in Surabaya from July to December 2020 with ARDS. The ROX indices were recorded at the 1st hour, 2nd, 4th, 6th, 12th, 18th, 24th, and 48th hours of treatment in ICU with HFNC. Identification of ROX association with HFNC failure led to intubation and 28-days mortality was through Cox proportional hazards regression. The most specific cut-off of the ROX index for predicting intubation and 28-days mortality was assessed.

Result: Among 78 patients who met the inclusion criteria, 26 (33.3%) patients required intubation. Out of 26 patients, six patients were extubated and had survived. The 28-days mortality rate is 20 (25.6%) patients. The ROX index at 12th hours (ROX-12) ≤ 4.85 (AUC 0.857; $p < 0.001$; HR 4.7) and the ROX index at 48th hours (ROX-48) ≤ 5.68 (AUC 0.858; $p < 0.001$; HR 5.4) can accurately predict the need for intubation. ROX-12 ≤ 4.745 is a predictor of 28-days mortality (AUC 0.85, $p < 0.001$; HR 10.2).

Conclusion: ROX index predicts the risk of intubation and 28-days mortality especially ROX-12 and ROX-48. Utilization of ROX index for rapid assessment of the respiratory deterioration in COVID-19 is recommended.

Keywords: ROX Index; HFNC; Intubation; ARDS; COVID-19

INTRODUCTION

Cases of pneumonia with the cause of coronavirus infection emerged in Wuhan, Hubei Province, China in late December 2019.[1] Since then, the number of cases has increased rapidly, marked by 44 new case reports in less than a week. In less than a month, this disease quickly spread to various provinces in China, Japan, South Korea, and Thailand.[2] WHO has officially named this disease coronavirus disease 2019 (COVID-19), which is caused by the Severe Acute Respiratory Disease Coronavirus-2 (SARS-CoV-2) virus.[3] This disease is a global health problem with a high rate of human-to-human transmission and has spread widely in China and 190 other countries.[4] Due to the high rate of infection transmission, WHO has declared COVID-19 as a world pandemic.[5] In Indonesia as of January 20, 2021, there were 927,380 active cases with a death rate of 26,590 cases (WHO Indonesia, 2020). The mortality rate in Indonesia is 2.8% and is one of the highest mortality rates in Southeast Asia.[6]

Most cases of COVID-19 patients experience dyspnea and respiratory deterioration due to acute hypoxemic respiratory failure (AHRF). Silent hypoxemia is a phenomenon characterized by a dissociation between oxygen saturation (SpO₂) and ventilatory dynamics in critically ill COVID-19 patients.[7, 8] Oxygen therapy is the first choice of management of COVID-19 related to AHRF.[9, 10] Non-invasive oxygen therapy such as non-invasive ventilation (NIV) or high flow nasal cannulae (HFNC) is well tolerated, and proven to be effective to treat hypoxemic respiratory failure.[11, 12] The reason for using HFNC is because it is effective, non-invasive, and more convenient.[13] Nevertheless, in critically-ill patients and severe ARDS, the HFNC/NIV most likely fail and the recommended course of action is invasive mechanical ventilation (IMV). Recent data show that the use of HFNC in COVID-19 was correlated with the lower need for intubation, shorter hospital length of stay (LOS), and lower mortality rates in comparison with standard oxygen therapy, but no different with NIV. [14-16]

These positive results followed physiological studies showing improved oxygen supply, elimination of physiologic dead-space of the upper airway, lung mechanics, and comfort associated with HFNC. [17, 18] COVID-19 pneumonia is the frequent cause of ARDS during the pandemic and this has led physicians to attempt this technique.

The main concern of the increasing use of HFNC in critically-ill COVID-19 ARDS is the risk of delaying needed intubation. Delayed intubation can lead to a worse outcome and prior death. Moreover, there are no validated and approved intubation criteria for COVID-19 associated with ARDS. These may lead to considerable differences among physicians in terms of the timing of intubation that could affect the outcome.[19] ROX is an index that can predict the risk of HFNC failure in severe pneumonia[12], yet it had not been validated to COVID-19 ARDS.[20] There are many different results between studies regarding the ROX cut-off to predict HFNC failure in COVID-19 and it remains debated.[20-22]

METHODS

This is a retrospective observational study. The data were recorded from medical records of COVID-19 patients admitted to ICU Dr. Soetomo General Hospital in Surabaya, Indonesia, from July to December 2020. Adult patients with the age of ≥ 18 years, confirmed COVID-19 by polymerase chain reaction (PCR) test, and the PaO₂/FiO₂ ratio < 300 mmHg were included. Patients with an immediate indication of intubation and/or rejecting treatment were excluded. We also excluded pregnant patients and incomplete medical records from this study. ROX indices were assessed at the 1st hour (ROX-1), 2nd (ROX-2), 4th (ROX-4), 6th (ROX-6), 12th (ROX-12), 18th (ROX-18), 24th (ROX-24), and 48th hours (ROX-48) during treatment in ICU. We used the ARDS criteria (Berlin's Criteria) based on the PaO₂/FiO₂ ratio to assess the severity of the respiratory failure [23]. Identification of ROX association with HFNC failure led to intubation and 28-days mortality was through Cox proportional hazards regression. We assessed the most specific cut-off of the ROX index to predict the risk of intubation and 28-days mortality.

This study was approved and obtained ethical clearance by the Ethical Committee of Clinical Research Unit, Dr. Soetomo General Hospital, Surabaya Number 0009/KEPK/VI/2020.

Statistical analysis of this study was conducted using IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 26th. Kolmogorov-Smirnov test is done for the normality test. Quantitative variables are presented as mean \pm standard deviation (SD), median (interquartile range). The categorical variables are presented as frequency (percentage). We used Student T-test or Mann-Whitney test to compare the continuous variables as appropriate. Pearson chi-square or Fisher exact test were assessed to find the differences between categorical variables. Receiver operating characteristic curves (ROCs) were performed to assess the accuracy of different variables for correctly classifying patients who would succeed or fail on HFNC. The areas under the curves (AUCs) were also calculated. ROX index's ability and cut-off to predict intubation and mortality were analyzed sensitivity, specificity, Positive Predicted Value (PPV), Negative Predicted Value (NPV), Likelihood Ratio positive (LR+), Likelihood Ratio negative (LR-) analysis. The relative risk (RR) of intubation and 28-days mortality were analyzed with the Pearson Chi-Square test. To identify if the ROX index was associated with the need for mechanical ventilation and 28-days mortality. Cox proportional hazards modeling was chosen to adjust other covariates simultaneously.

RESULT

A total of 78 eligible patients of COVID-19 with ARDS were treated with HFNC. Table 1 are presenting the baseline characteristics of participants. The median age is 47.7 years old and most of the participants are male. There are 20 obese patients and three morbidly obese patients. Diabetes and hypertension are the most comorbidities among the participants. 45 participants with moderate ARDS and 23 participants with severe ARDS. 26 patients were intubated after HFNC failure according to the clinical assessment of the attending physician. During treatment, six patients were successfully extubated after mechanical ventilation and discharged from the hospital while 20 patients did not survive.

TABLE 1: Baseline characteristics of the participants.

Characteristics	n=78 (%)	Mean (\pm SD) / Median (IQR)
Age (years)		47.75 (\pm 13.39) ^a
Sex		
Male	53 (66.3)	
Female	25 (33.3)	
Weight (kgs)		72 (63 – 85.75) ^b
BMI		26.42 (23.51 – 31.12) ^b
Normal	28 (36.3)	
Overweight	27 (33.8)	
Obesity	20 (26.3)	
Morbid Obesity	3 (3.8)	
Comorbidities		
Geriatric	10 (12.5)	
Diabetes	34 (42.5)	
Hypertension	6 (8.8)	
Cardiac disease	7 (8.8)	
Chronic lung disease	1 (1.3)	
Liver disease	8 (10)	
Neurological disease	3 (3.8)	
Chronic kidney disease	2 (2.5)	
Autoimmune disorder	1 (1.3)	

Characteristics	n=78 (%)	Mean (\pm SD) / Median (IQR)
SOFA Score		4 (3 – 4) ^b
PSI Score		66.45 (\pm 28.48) ^a
PaO2/FiO2 Ratio		125.5 (91.5 – 179) ^b
Awake Prone	23 (28.7)	
Post Ventilator	10 (12.5)	
ARDS Severity		
Mild ARDS	10 (12.5)	
Moderate ARDS	45 (56.3)	
Severe ARDS	23 (28.7)	
HFNC duration (hours)		109.6 (\pm 69.75) ^a
HFNC failure-intubated	26 (32.5)	
Survivor	6 (7.5)	
Non-survivor	20 (25)	
28-days mortality		
Survivor	58 (73.8)	
Non-survivor	20 (26.3)	
ICU LOS (days)		8.5 (6 – 15.75) ^b

^aMean (\pm SD)^bMedian (IQR)

Body Mass Index (BMI); Sequential Organ Failure Assessment (SOFA) score; Pneumonia Severity Index (PSI) score; Length of Stay (LOS)

The characteristics of participants with HFNC failure and success group as well as survivor and non-survivor group are shown in Table 2 and Table 3 respectively. The HFNC failure group shows a significant correlation in the age of the participants, higher initial SOFA scores, higher initial

PSI scores, lower initial PaO2/FiO2 ratio, ARDS severity, and Length of Stay (LOS) in ICU with a p-value of 0.012, 0.01, 0.016, 0.002, 0.019, and 0.001 respectively (Table 2). Meanwhile, the non-survivor group also shows a similar result (Table 3).

TABLE 2: Characteristics of participants based on HFNC success or failure.

Characteristics	HFNC success (n=52)	HFNC Failure-Intubated (n=26)	p-value
Age (years)	50.67 (\pm 12.92)	42.19 (\pm 12.93)	0.012 ^{a*}
Sex			
Male	36 (69.2)	17 (65.4)	0.732 ^c
Female	16 (30.8)	9 (34.6)	
Weight (kgs)	72 (62.5-87.25)	72 (63.75-85)	0.88 ^b
BMI	26.015 (23.52-31.67)	27.20 (23.16-29.56)	0.832 ^b
Normal	17 (32.7)	10 (38.5)	0.363 ^b
Overweight	16 (30.8)	11 (42.3)	
Obesity	16 (30.8)	5 (19.2)	
Morbid Obesity	3 (5.7)	0	
Comorbidities			
Geriatric	6 (11.5)	4 (15.4)	0.632 ^c
Diabetes	24 (46.1)	10 (38.5)	0.518 ^c
Hypertension	18 (34.6)	11 (42.3)	0.508 ^c
Cardiac disease	3 (5.8)	4 (15.4)	0.161 ^c
Chronic lung disease	1 (1.9)	0	0.477 ^c
Liver disease	5 (9.6)	3 (11.5)	0.792 ^c
Neurological disease	1 (1.9)	2 (7.7)	0.212 ^c
Chronic kidney disease	0	2 (7.7)	0.043 ^{c*}
Autoimmune disorder	1 (1.9)	0	0.477 ^c
SOFA Score	3.5 (3-4)	4 (4-5)	0.01 ^{b*}
PSI Score	62.6 (\pm 25.6)	77.42 (\pm 30.37)	0.016 ^{a*}
Initial PaO2/FiO2 Ratio	148 (108.75-186.5)	100 (69.75-143.5)	0.002 ^{b*}
Awake Prone	14 (26.9)	9 (34.6)	0.482 ^c
Post Ventilator	7 (13.5)	3 (11.5)	0.811 ^c
ARDS Severity			0.019 ^{c*}
Mild ARDS	8 (15.4)	2 (7.7)	
Moderate ARDS	34 (65.4)	11 (42.3)	
Severe ARDS	10 (19.2)	13 (50)	

Characteristics	HFNC success (n=52)	HFNC Failure-Intubated (n=26)	p-value
HFNC duration (hours)	121.13 (\pm 60.9)	90.54 (\pm 83.17)	0.090 ^{a*}
28-days Mortality			<0.001 ^c
Survivor	52 (100)	6 (23)	
Non-survivor	0 (0)	20 (77)	
LOS ICU (Days)	7.5 (5-10)	16.5 (11.25-23.25)	<0.001 ^{b*}
Initial Laboratory Finding			
D-dimer	1000 (642-2465)	1420 (807.5-3075)	0.170 ^b
Procalcitonin	0.145 (0.08-0.292)	0.27 (0.137-0.567)	0.037 ^{b*}
CRP	9.65 (2.77-14.9)	11.8 (6.47-14.7)	0.414 ^b
Lactate	1 (0.7-1.44)	1.22 (0.8-1.47)	0.435 ^b
pH	7.42 (7.39-7.46)	7.385 (7.318-7.45)	0.120 ^b
pCO ₂	36.5 (29.9-44)	36.35 (30.45-45)	1.0 ^b

^aMean (\pm SD) with Independent Samples t-test, p-value <0.05

^bMedian (IQR) with Mann-Whitney test, p-value <0.05

^cChi-square test; *p-value <0.05 was significantly correlated

TABLE 3: Characteristics of the survivor and non-survivor participants.

Characteristics	Survivor (n=58)	Non-survivor (n=20)	p-value
Age (years)	49.4 (\pm 13.8)	42.8 (\pm 10.7)	0.051 ^a
Sex			
Male	39 (67.2)	14 (70)	0.820 ^c
Female	19 (32.8)	6 (30)	
Weight (kgs)	74 (63-90)	70 (62.5-77)	0.262 ^b
BMI	26.08 (23.51-31.24)	27.68 (23.28-30.91)	0.785 ^b
Normal	20 (34.5)	7 (35)	0.231 ^c
Overweight	17 (29.3)	10 (50)	
Obesity	18 (31)	3 (15)	
Morbid Obesity	3 (5.2)	0 (0)	
SOFA Score	4 (3-4)	4 (4-5)	0.010 ^{b*}
PSI Score	61.7 (\pm 26.4)	79.6 (\pm 30.5)	0.013 ^{a*}
PaO₂/FiO₂ Ratio	140 (107-194)	106 (69.5-138)	0.005 ^{b*}
Awake Prone	17 (29.3)	6 (30)	0.953 ^c
Post Ventilator	7 (12.1)	3 (15)	0.735 ^c
ARDS Severity			0.053 ^c
Mild ARDS	9 (15.5)	1 (5)	
Moderate ARDS	36 (62.1)	9 (45)	
Severe ARDS	13 (22.4)	10 (50)	
HFNC duration (hours)	113.4 (\pm 62.3)	98.8 (\pm 88)	0.413 ^a
HFNC success/failure			<0.001 ^{c*}
HFNC failure/intubated	6 (10.3)	20 (100)	
HFNC success	52 (89.7)	0 (0)	
Time to intubate (hours)	57 (30.25-105.25)	72.5 (32.5-140.25)	0.648 ^b
LOS ICU (days)	8 (5-11)	14 (8-19.5)	0.007 ^{b*}
Comorbidities			
Geriatric	7 (12.1)	3 (15)	0.735 ^c
Diabetes	25 (43.1)	9 (45)	0.883 ^c
Hypertension	20 (34.5)	9 (45)	0.401 ^c
Cardiac disease	4 (6.9)	3 (15)	0.274 ^c
Chronic lung disease	1 (1.7)	0 (0)	0.555 ^c
Liver disease	6 (10.3)	2 (10)	0.933 ^c
Neurological disease	1 (1.7)	2 (10)	0.097 ^c
Chronic kidney disease	0 (0)	2 (10)	0.015 ^{c*}
Autoimmune disorder	1 (1.7)	0 (0)	0.555 ^c
Initial Laboratory Finding			
D-dimer	1130 (650-2820)	1280 (785-2760)	0.394 ^b
Procalcitonin	0.16 (0.09-0.34)	0.26 (0.11-0.595)	0.143 ^b
CRP	10.1 (3.1-14.8)	8.3 (4.25-14.9)	0.943 ^b
Lactate	1.0 (0.7-1.3)	1.35 (0.85-1.5)	0.168 ^b
pH	7.42 (7.38-7.46)	7.41 (7.315-7.445)	0.194 ^b
pCO ₂	36.7 (29.6-44)	36.2 (31.25-44)	0.943 ^b

^aMean (±SD) with Independent Samples t-test, p-value <0.05
^bMedian (IQR) with Mann-Whitney test, p-value <0.05
^cChi-square test, *p-value <0.05 was significantly correlated.

ROX index's ability as a predictor of HFNC failure that led to intubation and 28-days mortality are listed in Table 4. ROX index in each hour has significant results in predicting the intubation and 18-days mortality, both with a p-value of 0.001).

ROX-12 and ROX-48 have the highest AUC both in predicting intubation (0.857 and 0.858 respectively) and 28-days mortality (0.858 and 0.853 respectively) (Figure 1). Thereafter, Table 4 also showed ROX-12 and ROX-48 have the highest relative risk (RR) predicting the risk of intubation and 28-days mortality 8.448 and 7.0; 7.556 and 6.667 respectively.

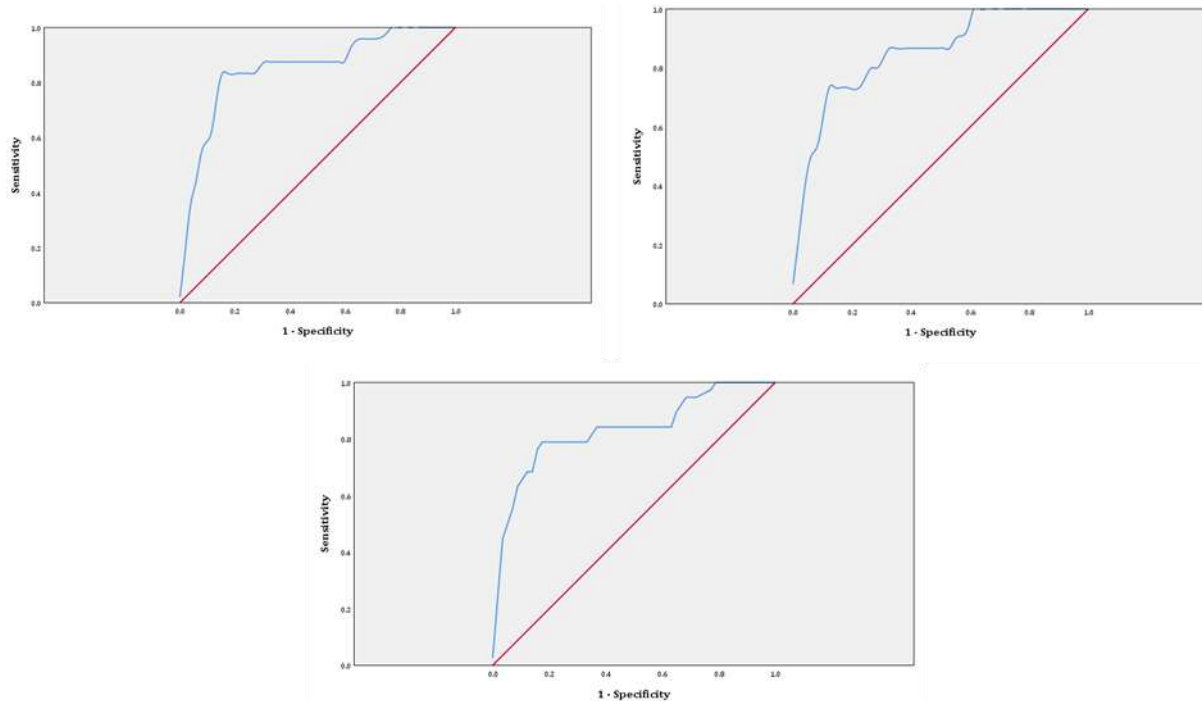


FIGURE 1: The ROC test analysis of ROX index at hour 12th (A) and hour 48th (B) on the incidence of intubation, and the ROX index at hour 12th (C) of 28-days mortality.

The most specific cut-off of the ROX index to predict intubation and 28-days mortality were both ROX-12 and ROX-48. Cox proportional hazards regression adjusted with other ROX indices. The results are both ROX-12 and

ROX-48 can be used as a predictor of intubation in COVID-19 ARDS. Also, ROX-12 with different cut-off points (≤ 4.745) can be used as a predictor of 28-days mortality (Table 5).

TABLE 4 : Sensitivity, Specificity, PPV, NPV, LR+, and LR- of ROX Index in finding the risk of Intubation and 28-days Mortality.

ROX index	Cut-off	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	RR	p-value
Hour-1										
Intubation	4.54	0.760	73.08	74.07	57.58	85.11	2.82	0.36	3.866	<0.001*
Mortality	4.49	0.795	71.43	72.88	48.39	87.76	2.63	0.39	3.952	0.001*
Hour-2										
Intubation	4.74	0.769	73.08	72.22	55.88	84.78	2.63	0.37	3.672	<0.001*
Mortality	4.49	0.800	76.19	77.97	55.17	90.20	3.46	0.31	5.628	<0.001*
Hour-4										
Intubation	4.65	0.746	69.23	70.37	52.94	82.61	2.34	0.44	3.044	0.001*
Mortality	4.56	0.762	71.43	71.19	46.87	87.50	2.48	0.40	3.750	0.001*
Hour-6										
Intubation	4.72	0.772	76.92	75.93	60.61	87.23	3.20	0.30	4.747	<0.001*
Mortality	4.48	0.763	71.43	72.88	48.39	87.76	2.63	0.39	3.952	0.001*
Hour-12										
Intubation	4.85	0.857	83.33	83.33	68.97	91.84	5.0	0.20	8.448	<0.001*
Mortality	4.745	0.858	80.0	81.03	59.26	92.16	4.22	0.25	7.556	<0.001*
Hour-18										
Intubation	5.16	0.830	75.0	74.07	56.25	86.96	2.89	0.34	4.313	<0.001*
Mortality	5.04	0.819	75.0	74.14	50.0	89.58	2.90	0.34	4.80	<0.001*
Hour-24										
Intubation	4.925	0.777	56.52	81.48	56.52	81.48	3.05	0.53	3.052	0.001*
Mortality	5.255	0.796	73.68	74.14	48.28	89.58	2.85	0.35	4.634	0.001*

ROX index	Cut-off	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	RR	p-value
Hour-48										
Intubation	5.68	0.858	80.0	76.47	50.0	92.86	3.40	0.26	7.0	<0.001*
Mortality	5.525	0.853	76.92	77.36	45.45	93.18	3.40	0.3	6.667	0.001*

*p-value <0.05 are significantly correlated; ROC curves; Pearson Chi-Square was used.

TABLE 5: Cox Proportional Hazards Regression of ROX Index Predicting Intubation and 28-Days Mortality

ROX index	Intubation				28-days Mortality			
	HR	Corr. Coefficient	95% CI	p-value	HR	Corr. Coefficient	95% CI	p-value
Hour-1	-	-	-	0.545	-	-	-	0.142
Hour-2	-	-	-	0.237	-	-	-	0.123
Hour-4	-	-	-	0.930	-	-	-	0.184
Hour-6	-	-	-	0.335	-	-	-	0.253
Hour-12	4.707	1.549	1.389 – 15.945	0.013*	10.286	2.331	2.774 – 38.132	<0.001*
Hour-18	-	-	-	0.728	-	-	-	0.996
Hour-24	-	-	-	0.264	-	-	-	0.964
Hour-48	5.469	1.699	1.424 – 21.011	0.013*	-	-	-	0.081

*p-value <0.05 are significantly correlated; Cox proportional hazards regression forward LR test.

DISCUSSION

The respiratory complication of SARS-CoV2 viral infection can lead to ARDS. ARDS related to COVID-19 shows an unusual phenotype and different characteristics from classic ARDS. There is a dissociation between the hypoxemia severity and the relatively good respiratory mechanics which are called silent hypoxemia.[7, 24] Silent hypoxemia potentially causes prolonged hypoxemia, and thus rapid and precise clinical assessment and treatment become necessary.

Predicting the outcome of critically-ill COVID-19 patients treated with HFNC is a major challenge for every physician. HFNC is a non-invasive oxygen treatment that is effective and excels in patients' comfort in comparison to NIV. Compared to standard oxygen therapy and NIV, HFNC showed better results for lower intubation rates in patients with PaO₂/FiO₂ ≤ 200 mmHg.[25] HFNC can prevent patient self-induced lung injury (P-SILI) by improving oxygenation and reducing the work of breathing[11, 17] The main concern regarding the use of non-invasive oxygen therapy of COVID-19 patients is delayed intubation.[26, 27] Consistent data shows that delayed or late intubation may worsen the outcome of patients with respiratory failure[28-30] and many suggest that early intubation seems to be the best course of action. Interestingly in COVID-19 respiratory failure, there are controversies about the timing of intubation. The right timing of intubation is a matter of great importance, but it is difficult to determine and there are not yet validated criteria for COVID-19 intubation. A recent study shows that there are no significant differences in mortality rates between the 'early' versus 'late' intubation.[16, 31] These findings suggest that the 'wait-and-see' may be the best approach for deciding the timing to intubate.

In this study, we established that ROX-12 ≤ 4.85 and ROX-48 ≤ 5.68 are a predictor of HFNC failure, while ROX-12 ≤ 4.745 predicts 28-days mortality. Additionally, we provide high sensitivity and specificity of specific cut-off points of the ROX index allowing identification of patients who need to be intubated and predicting the 28-days mortality within the first 12 hours of treatment with HFNC. These results may have the potential to improve practices in the monitoring and treatment of COVID-19 patients treated with HFNC. COVID-19 patients with the ROX index below the cut-off value (ROX-12 ≤ 4.745) have a greater risk of 28-days mortality by 7.5 times compared to the patients

with the ROX index above the cut-off value. Thus, it is recommended to re-evaluate the need to intubate to prevent prolonged hypoxemia and worse outcome.

Numerous studies have different cut-off values of the ROX index.[22, 32, 33] This may be due to differences in samples, data collection methods, data processing methods, and patient treatments. The experience and the decision-making of the physician in charge may also vary. Therefore, it is difficult to determine a uniform cut-off value due to the different variability. ROX index in COVID-19 are widely used and yet it somewhat differs from the proposed cut-off point by Roca.[12] Studies in several countries reported that cut-off points <5 in the first 12-hours of treatment were strongly associated with HFNC failure that can lead to intubation and mechanical ventilation.[21, 22] Study in Egypt measuring the ROX index to predict the intubation in COVID-19 patients on day 1 to day 3 reported that ROX index at day 3 to hour-72 has cut-off point ≤ 11.71, sensitivity 90%, specificity 100%, PPV 100%, NPV 87.5% and AUC 0.975.[33]

Data from our studies regarding the time of intubation shows that most intubations occur between the first 12th and the 48th hour. We, therefore recommend monitoring the ROX index over time with a focus from the 12th hour ahead: the risk of failure is high if less than 4.85, and intubating the patient should be considered. Interestingly, there are two cut-off points in ROX-12 in this study, A zone exists between 4.745 and 4.85. It may suggest if the patient ROX index is between 4.745 and 4.85, then the patient is at risk of HFNC failure but not yet at risk for 28-days mortality. Further study needs to be conducted to confirm this opinion. To our knowledge, this is the first study to assess the ROX prognostic ability for 28-days mortality in COVID-19.

Our study has several limitations. First, COVID-19 confirmed participants in this study are based on the result of a positive PCR. PCR is considered to be the gold standard of the confirmed COVID-19 diagnostic,[34, 35] but we cannot dismiss the existence of false-positive and/or false-negative results. Second, because there is yet no validated or standardization of intubation criteria specific for COVID-19 with ARDS, and the outcome of mechanical ventilation might be somewhat subjective.

Third, the sample collected in this study may not represent the population affected by the pandemic, especially the collected data from the first wave of the pandemic in Surabaya, Indonesia. Fourth, the data extractors were not blinded and may be biased in interpreting the data. Finally, this is a retrospective study with the methodological drawbacks it may entail.

CONCLUSION

ROX index is a useful means to predict HFNC failures leading to intubation (ROX-12 and ROX-48) and 28-days mortality (ROX-12). The ROX index is non-invasive, simple, particularly useful to identify the risk for respiratory deterioration and to assist therapeutic decisions. Therefore, utilization of the ROX index is recommended for the rapid assessment in critically-ill COVID-19 patients.

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