REUE | Original Article

ROX index for predicting early intubation in patients with COVID-19 treated with low-flow oxygen

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OBJECTIVE. To determine a cut point for the ROX index (ratio of peripheral oxygen saturation to the fraction of inspired oxygen) as a predictor of early intubation in patients with COVID-19 in treatment with a low-flow oxygen oxygen system.

METHODS. Retrospective case-control study of patients hospitalized for SARS-CoV-2 requiring treatment with low-flow oxygen. Case patients were those who later required intubation; control patients were those who did not. We collected demographic and clinical data, including blood gas variables for calculating the ROX index. Descriptive and inferential statistics were also calculated. The ROX index cut point at 6 hours of low-flow oxygen supplementation was determined by Youden's J statistic on the receiver operating characteristic (ROC) curve.

RESULTS. Of 192 patients reviewed, 144 (62 cases and 82 controls) met the inclusion criteria. A ROX index cut point of 5.71 was selected. At that point, sensitivity was 84% (95% CI, 73.2-92.5) and specificity was 90.3% (95% CI, 81.6-95.6). The positive and negative predictive values, respectively, were 78% (95% CI, 68%-87%) and 97% (95% CI, 89%-99%). The area under the ROC was 0.94 (95% CI, 0.90-0.97) for predicting that a patient on low-flow oxygen would come to need more advanced airway management.

CONCLUSIONS. The ROX index proved to be a useful tool for predicting progression to advanced airway management in patients with SARS-CoV-2 treated with low-flow oxygen. The cut point of 5.71 was higher than the established point for switching to high-flow nasal cannula systems.

Keywords: ROX index. COVID-19. Intubation.

El índice de ROX como predictor de intubación temprana en pacientes con COVID-19 tratados con oxigenoterapia de bajo flujo

OBJETIVO. Determinar un punto de corte del índice ROX (iROX) relacionado con la necesidad de intubación temprana, en pacientes con COVID-19 en tratamiento con dispositivos de oxigenación de bajo flujo (DOBF).

MATERIAL Y MÉTODOS. Estudio retrospectivo, en pacientes que requirieron ser hospitalizados debido a la infección por SARS-CoV-2, y que recibieron tratamiento con DOBF. Los pacientes fueron divididos en dos grupos: casos, pacientes que posteriormente requirieron intubación, y controles, aquellos que no requirieron este tipo de soporte. Se recopilaron datos demográficos, clínicos y parámetros gasométricos para calcular el iROX. El punto de corte del iROX a las 6 horas desde el inicio del manejo con oxígeno suplementario se determinó mediante el índice de Youden en la curva ROC.

RESULTADOS. De 192 pacientes, 144 cumplieron con los criterios de inclusión (62 en el grupo casos y 82 en el grupo control). Se obtuvo un punto de corte de < 5,71 para el iROX [con sensibilidad 84% (IC 95%: 73,2-92,5), especificidad 90,3% (IC 95%: 81,6-95,6), VPP 78% (IC 95%: 68-87), VPN 97% (IC 95%: 89-99) y área bajo la curva ROC de 0,94 (IC 95%: 0,90-0,97], para predecir que el paciente con DOBF requiere de manejo avanzado de la vía aérea.

CONCLUSIONES. El iROX resultó ser una herramienta eficaz para predecir la progresión hacia el manejo avanzado de la vía aérea en pacientes con infección por SARS-CoV-2 bajo tratamiento con DOBF. El punto de corte identificado < 5,71 resultó ser mayor al establecido para las cánulas nasales de alto flujo.

Palabras clave: Índice ROX. COVID-19. Intubación.

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Introduction

The disease caused by SARS-CoV-2 infection, known as COVID-19, affects the respiratory tract and presents with manifestations ranging from mild illness to severe acute respiratory distress syndrome (ARDS).[1] In Mexico, the pandemic began in 2020, revealing the limitations of a health care system that had not achieved universal coverage and became overwhelmed by patient demand.[2,3] To reduce respiratory symptoms and improve prognosis, respiratory support became vital. Among the noninvasive mechanical ventilation (NIV) devices, high-flow nasal cannula (HFNC) therapy stands out.[4,5] To improve the ability to distinguish between patients who would succeed or fail with HFNC therapy, a clinical indicator known as the respiratory rate–oxygenation (ROX) index was proposed. The ROX index is defined as the ratio between oxygen saturation (SpO_2) / fraction of inspired oxygen (FiO_2, %) and respiratory rate (RR, breaths/min). A ROX index < 4.88, measured after 6 hours of HFNC use, has been significantly associated with a higher risk of requiring invasive mechanical ventilation.[6,7] During the pandemic, limited availability of HFNC led to the use of low-flow oxygen devices (LFOD), such as reservoir masks. The objective of this study was to establish a cutoff value for the ROX index at 6 hours of LFOD therapy and to determine its predictive capacity for subsequent intubation.

Material and methods

We conducted a retrospective study in a secondary-level hospital in Metepec, Puebla, Mexico, from February 2020 to February 2021. Patients older than 18 years—both men and women—admitted to the COVID-19 isolation area who met the operational definition of a confirmed COVID-19 case were included. In 2020, confirmation was based on RT-PCR testing, and in 2021, on rapid antigen testing. Patients who required LFOD during the first 6 hours after admission were selected. Patients were categorized into 2 groups: the case group included patients with failed LFOD treatment and subsequently required early intubation (placement of an endotracheal tube in a critically ill patient) within the first 6–12 hours of therapy. The control group included patients who received LFOD therapy without progressing to intubation within the same period. Exclusion criteria included incomplete health records, advanced airway management upon admission, and chronic lung disease. From health records, data were collected on sex, age, comorbidities, vital signs, oxygen saturation, and fraction of inspired oxygen to calculate the ROX index after 6 hours of LFOD use. Descriptive and inferential statistics were applied, with statistical significance set at $P < .05$. Receiver operating characteristic (ROC) curves were used to determine the optimal ROX cutoff value using the Youden index (sensitivity, specificity, and area under the curve [AUC]), as well as positive predictive value (PPV) and negative predictive value (NPV). Statistical analyses were performed using GraphPad Prism 5.0 and R Core Team software. The study was approved by the institutional ethics and research committee (Registry R-2021-2106-015).

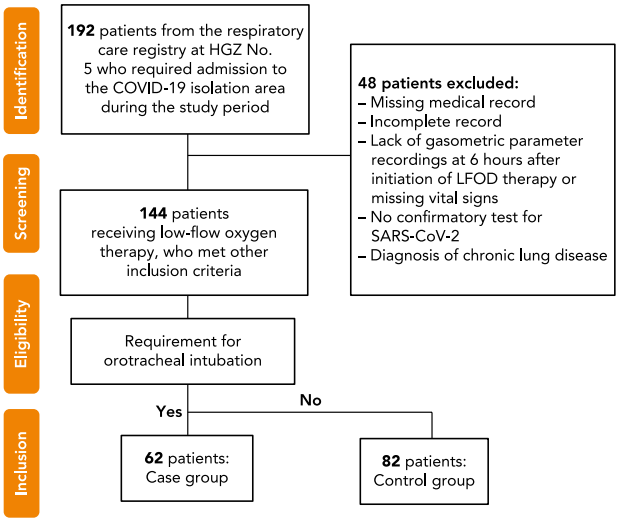

Figure 1. Flowchart of patient selection for the study "The ROX Index as a Predictor of Early Intubation in Low-Flow Oxygen Therapy for COVID-19."
LFOD: low-flow oxygen devices.

Results

Data from 192 patients admitted to the COVID-19 isolation area were reviewed; 144 met the inclusion criteria (67 women and 77 men). Of these, 62 were categorized in the case group and 82 in the control group; a total of 48 patients were excluded (Figure 1). The mean age for all patients was 57.7 years. The case group had a higher mean age than the control group ($P = .001$) and included 58% men with a mean age of 69.2 years ($P = .006$). No significant differences in sex or age were found in the control group. The presence of comorbidities was similar in both groups ($P > .05$) (Table 1).

Regarding the type of LFOD used, the reservoir mask was predominant in the case group (98.3%) ($P = .0001$), whereas simple nasal cannulas were most common in the control group (40.2%) ($P = .0001$) (Table 1). Statistically significant differences were observed in the gasometric parameters used to calculate the ROX index (SpO_2, FiO_2, and RR) between groups ($P < .001$) (Table 1). A ROX cutoff value for predicting intubation in patients using LFOD was determined using the Youden index: < 5.71, with a sensitivity of 84% 95% CI, 73.2–92.5), specificity of 90.3% (95% CI, 81.6–95.6), and an AUC of 0.94 (95% CI, 0.90–0.97) (Figure 1). The PPV was 78% (95% CI, 68–87) and the NPV was 97% (95% CI, 89–99) (Figure 2). In the multivariate analysis, variables such as male sex, age > 57.8 years, male age > 69 years, and presence of comorbidities were not associated with early intubation. However, a ROX index < 5.71 was associated with a higher likelihood of requiring intubation in 60 patients, compared with 51 patients who had a ROX index < 4.88 (Table 2).

Discussion

Our results establish a cutoff value of < 5.71 at 6 hours after initiating LFOD therapy, identifying treatment failure and the need for invasive mechanical ventilation. This val-

Table 1. Comparison of demographic and clinical variables between the case group and control group of patients on low-flow oxygen devices therapy 6 hours after admission to the COVID-19 isolation area

	All Patients	Case Group	Control Group	*P*-value
Gender	n (%)	n (%)	n (%)	
Male	77 (53)	36 (58)	41 (50)	> .05
Female	67 (47)	26 (42)	41 (50)	> .05
Total	144 (100)	62 (100)	82 (100)	
	$\bar{x}$ (± SD)	$\bar{x}$ (± SD)	$\bar{x}$ (± SD)	
Age (years)	57.7 (17.3)	64 (17)	52 (15.3)	.001
Female age	55.7 (15.0)	57.7 (12.8)	54.5 (16.3)	> .05
Male age	59.3 (19.3)	69.2 (15.4)	50.7 (17.7)	.005
Comorbidities	n (%)	n (%)	n (%)	
None	62 (43.2)	21 (34.0)	41 (50.0)	> .05
T2DM or SAH	58 (40.2)	27 (43.0)	31 (37.8)	> .05
T2DM and SAH	20 (13.8)	10 (16.0)	10 (12.2)	> .05
T2DM, SAH, other	4 (2.8)	4 (7.0)	0 (0)	> .05
Total	144 (100)	62 (100)	82 (100)	
LFOD Type				
Reservoir mask	103 (71.5)	61 (98.3)	42 (51.2)	.0001
Simple nasal cannula	34 (23.6	1 (0.7)	33 (40.2)	.0001
Simple face mask	7(4.9)	0 (0.0)	7 (8.6)	.001
Total	144 (100)	62 (100)	82 (100)	
Parameters used to calculate ROX index 6 hours after admission to the COVID-19 isolation area				
SpO_2 (%)	86.7 (11.1)	77 (11.3)	93 (3.24)	.0001
FiO_2 (%)	61 (21.0)	78 (10.2)	49 (19.2)	.0001
RR (breaths/min)	24.3 (4.6)	26.9 (5.4)	22.3 (2.5)	.001
ROX index	7.8 (4.6)	4.0 (1.5)	10.2 (4.3)	.0001
HR (beats/min)	81.9 (16.6)	87.8 (18.6)	77.4 (13.4)	.0003

$\bar{x}$: mean; > $\bar{x}$: greater than the mean; T2DM: type 2 diabetes mellitus; SAH: systemic arterial hypertension; x (± SD): mean (± standard deviation); LFOD: low-flow oxygen devices; SpO_2: oxygen saturation (%); FiO_2: fraction of inspired oxygen (%); RR: respiratory rate (breaths per minute); ROX index = (SpO_2 / FiO_2) / RR; HR: heart rate (beats per minute).

ue is higher than the established cutoff for failure with hHFNC therapy (< 4.88 at 6 hours).[6,8] Recent studies have proposed new ROX index cutoffs for HFNC (2–6 hours < 4.88; 6–12 hours < 4.82),[9] and < 5.88 at 12 hours, which showed better performance for HFNC than the original < 4.88 threshold.[10]

During the editorial review of the present study, another publication reported a cutoff value of < 5.35 at 12 hours after initiating LFOD therapy in Mexican patients, with an

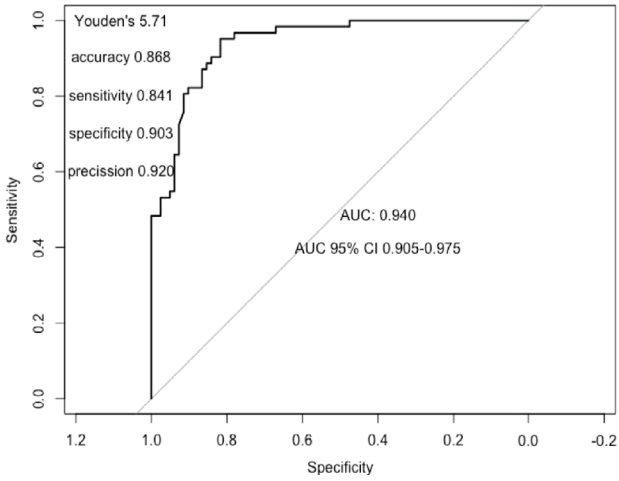

Figure 2. ROX index cutoff < 5.71 for predicting intubation in COVID-19 patients treated with LFOD 6 hours after admission to the COVID-19 isolation area, determined using the Youden index in a ROC curve.

AUC of 0.87.[11] In both a retrospective cohort study[12] and a prospective cohort study,[6] the ROX index calculated after 6 hours of oxygen therapy demonstrated good predictive capacity for success, proving highly valuable for identifying patients who would require invasive ventilatory support and preventing complications due to delayed intubation.

The mean age and sex distribution of patients in the case group were similar to those reported in studies of patients treated with HFNC who subsequently required intubation, with mean ages of 60 and 66.3 years, respectively.[13,14] A recent study involving LFOD patients reported a mean age of 62 years.[11] Regarding sex, no significant differences were found vs other ROX index studies.[11,13] The prevalence of comorbidities in our cohort was consistent with previous findings, showing a higher frequency of type 2 diabetes and systemic arterial hypertension. Other studies—including cases with renal failure and breast cancer at lower rates—also found that comorbidities did not affect the ROX index's ability to predict early intubation.[13-15] In our study, comorbidities and age variability did not influence the ROX cutoff value among patients using LFOD.

Table 2. Uni- and multivariate analysis of variables associated with early intubation in COVID-19 patients on LFOD 6 hours after admission to the COVID-19 isolation area

Variables associated with intubation	Patients		Univariate analysis		Multivariate analysis	
	N	Intubated	OR	*P*-value	OR	*P*-value
Male sex	77	36	1.38 (0.7-2.6)	.399	NA	NA
Age > 57.8 years	78	44	3.4 (1.7-6.9)	.001	2.0 (0.31-13)	.113
Male > 59.3 years	46	27	2.7 (1.3-5.7)	.012	1.7 (0.21-13.9)	.939
Presence of comorbidities	82	41	1.9 (0.98-3.8)	.36	NA	NA
SpO_2 < 86.7%	53	51	185 (39-871)	.0001	44 (7.0-284)	.0001
FiO_2 > 62.5%	80	58	39 (12.8-121)	.0001	1.3 (0.09-20.3)	.960
RR > 24.5 breaths/min	43	34	9.8 (4.1-23.8)	.0001	2.4 (0.38-14.8)	.248
ROX index < 4.88	58	51	49 (18-136)	.0001	1.3 (0.14-11.7)	.745
ROX index < 5.71	76	60	118 (2.1-4480)	.0001	14.3 (3.1-448)	.002
HR > 81 bpm	66	38	3.7 (1.5-6.0)	.001	9.3 (1.5-57)	.008

LFOD: low-flow oxygen devices; $\bar{x}$: mean; SpO_2: oxygen saturation (%); FiO_2: fraction of inspired oxygen (%); RR: respiratory rate (breaths per minute); HR: heart rate (beats per minute); NA: non-applicable.

When comparing gasometric parameters between groups, we observed significant differences: the case group showed lower ROX index values, higher FiO_2 requirements, and increased respiratory and heart rates, likely reflecting the metabolic response to infection.[16]

Study limitations

The sample size was calculated assuming that, in Mexico, 9.6% of patients with COVID-19 require intubation, which limited the size of the case group in our study due to the exclusive use of lLFOD. Because this was a retrospective study, the correct use of oxygen therapy devices and the accuracy of data recording could not be guaranteed. In addition, the exclusion of cases with incomplete medical records further limited the sample size. The subsequent clinical course of patients was not followed to determine outcomes among those who were intubated early, which prevented the use of this cohort to assess the impact on mortality.

The ROX index in this study was determined in patients with COVID-19; therefore, the same cohort value cannot yet be assumed for other types of pneumonia when using LFOD.

In conclusion, a ROX index with a cutoff value of < 5.71 is a useful tool for predicting early intubation in patients treated with LFOD. Larger and comparative studies involving other respiratory diseases in emergency department settings are needed.

ARTICLE INFORMATION

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