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LETTER

ROX index to predict CPAP outcome in hypoxemic respiratory failure due to COVID-19

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Dear Editor,

In hypoxemic patients undergoing noninvasive support, strict clinical monitoring is essential to early detect treatment failure, avoid the occurrence of self-inflicted lung injury, and not delay endotracheal intubation and protective ventilation. In patients undergoing high-flow nasal oxygen, the respiratory rate oxygenation (ROX) index has been proposed and shown to accurately identify patients likely to require endotracheal intubation within 12 h from treatment onset [1]. This is an easy-to-use, bedside available index that normalizes SpO_2/FiO_2 to respiratory rate.

Continuous positive-airway pressure (CPAP) has been recently shown to improve the clinical outcome of patients suffering from hypoxemic respiratory failure due to coronavirus disease 2019 (COVID-19) [2]. There is paucity of validated tools to identify treatment failure when hypoxemic patients are treated with CPAP, while any delay in intubation should be avoided in this context as well.

We hereby report the results of a secondary analysis of a prospective cohort study conducted on patients who received CPAP due to severe COVID-19: the study was conducted in Hospital General de Agudos Juan A. Fernández, Buenos Aires, Argentina. Institutional review board reviewed the protocol and authorized prospective data collection (Code register: 2263). All patients provided informed consent to trial participation [3].

The aim of this analysis is to determine the reliability of ROX index to predict treatment failure during CPAP. Treatment failure was defined as the need for intubation, which was performed according to predetermined criteria not including ROX index [3]. ROX index was measured 2, 6, 12 and 24 h after CPAP treatment institution.

To evaluate the accuracy of ROX index in predicting the need for intubation, receiver operating characteristics (ROC) curves were used: area under the curve (AUC), sensitivity and specificity are displayed for each timepoint. For each timepoint, delta ROX (the change in ROX from the value measured at 2 h) was also evaluated. Best cut-off values were determined using the Youden's J statistic (J max).

From June 2020 to September 2021, 112 consecutive COVID-19 patients who received CPAP were included in the statistical analysis. Before CPAP start, while on high-flow nasal oxygen, median [IQR] PaO_2/FiO_2 was 98 [88–110], and median respiratory rate was 30 breaths/minute [26–34]. CPAP was delivered through a facemask connected to an intensive care unit ventilator with a non-vented circuit, or a helmet connected to a high-flow generator and a positive end-expiratory pressure (PEEP) valve. Median PEEP was 12 [10–14] cmH_2O. Forty-four (39%) patients required intubation, with a median time-to-intubation of 2 days [1–5].

As shown in Table 1, accuracy of ROX index in predicting the need for intubation increased over time, but sensitivity and specificity were essentially poor before 24 h from CPAP institution. At 24 h, instead, ROX index

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Table 1 Accuracy (area under the curve—AUC), sensitivity and specificity of ROX index and Delta ROX Index in discriminating CPAP failure at 2, 6, 12 and 24 h after treatment start

ROX Index	AUC	Cut-off	Youden's Index	Sensitivity	Specificity
2 h CPAP treatment	0.63	7.20	0.20	76	43
6 h CPAP treatment	0.71	6.32	0.44	89	54
12 h CPAP treatment	0.71	6.71	0.34	91	42
24 h CPAP treatment	0.94	6.64	0.74	97	75
Delta ROX index 2–6 h	0.58	0.25	0.27	48	78
Delta ROX index 2–12 h	0.60	− 0.45	0.22	66	55
Delta ROX index 2–24 h	0.83	0.18	0.56	67	88

showed an AUC of 0.94, with the best threshold of 6.64 [specificity 75% and sensitivity 97%].

These results suggest that, in COVID-19 hypoxemic respiratory failure, ROX index is an accurate predictor of treatment failure solely when evaluated after 24 h of CPAP treatment. This differs from what was reported in patients undergoing high-flow nasal oxygen, in whom ROX index has acceptable accuracy within 12 h of treatment [1, 4]. Also, the identified cut-off for predicting failure is higher than what was described for high-flow nasal cannula. 6.64 in our study vs. 3.85 in non-COVID-19 patients [1] and 5.37 in COVID-19 patients [4] undergoing high-flow nasal oxygen. Both these results may be related to the well-documented positive effect of positive-airway pressure on arterial oxygenation, which, however, may be falsely reassuring and not predictive of treatment success, especially in COVID-19 patients [5].

In conclusion, among patients with hypoxemic respiratory failure due to COVID-19, ROX Index < 6.64 after 24 h of CPAP shows excellent accuracy in predicting treatment failure and may be used to avoid delays in endotracheal intubation. Caution is needed when interpreting ROX values soon after CPAP institution, as they may not represent accurate predictors of treatment outcome.

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Author contributions
NCA and DLG conceived the study. NCA, MCS and GCM contributed to data acquisition and conducted statistical analysis. NCA interpreted the data and wrote the first draft of the manuscript. DLG and OR critically revised the manuscript. All the authors reviewed the final draft of the manuscript and agreed on submitting it to Intensive Care Medicine.

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Declarations

Conflicts of interest
DLG has received payments for travel expenses by Getinge and Air Liquide, speaking fees by Intersurgical, Gilead, Pfizer, General Electric Healthcare and Fisher & Paykel, and discloses a research grant by General Electric Healthcare. OR reported a research grant from Hamilton Medical AG, speaker fees from Hamilton Medical AG, Fisher & Paykel Healthcare Ltd, Aerogen Ltd and Ambu, and non-financial research support from Timpel; all outside the submitted work. The other authors have disclosed no conflicts of interest.

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