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LETTER

Role of PEEP on the prognostic performance of the ROX index in hypoxemic respiratory failure due to COVID-19: any further gain in outcome prediction?

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Dear Editor,

We read with great interest the Letter by Colaianni-Alfonso et al. on the use of respiratory rate oxygenation (ROX) index to predict outcome in patients receiving continuous positive airway pressure (CPAP) due to pneumonia caused by coronavirus disease 2019 (COVID-19) [1].

The ROX index has been proposed as an easy-to-use tool to monitor the hypoxemic patients undergoing non-invasive ventilatory assistance (NIV) with high-flow nasal oxygen (HFNO). It has been demonstrated that ROX index predicts treatment failure and need for endotracheal intubation within 12 h from HFNO onset [2].

NIV, including helmet CPAP, has been widely used during COVID-19 pandemic, even outside the intensive care units (ICUs) [3]. NIV bears several advantages, but the lack of monitoring of tidal volume and transpulmonary pressure carries the risk of patient self-inflicted lung injury (P-SILI). Therefore, identifying patients at risk of treatment failure and avoiding intubation are important elements of NIV.

The ROX index has been initially described for HFNO, and one could reason that once positive end expiratory pressure (PEEP) is applied, this should be considered to improve the accuracy of the index. For example, the same SpO_2/FiO_2 ratio might indicate a worst lung impairment for increasing levels of PEEP. The aim of this analysis is to evaluate whether the effect of incorporating the set PEEP in the already known ROX index improves its predictive performance in patients undergoing NIV.

We defined the PROX (pressure respiratory rate-oxygenation) index as the ratio between an oxygenation parameter, assessed by SpO_2/FiO_2, and the product of respiratory rate (RR) and PEEP.

Here, we report the results of a secondary analysis, merging novel data from a monocentric observation study conducted on patients admitted to the emergency department of Hospital San Gerardo (Monza, Italy) and a multicentric observational study [3] during COVID-19 pandemics. All the patients were diagnosed with COVID-19 pneumonia and were treated with noninvasive respiratory support outside the ICU. Local ethics committees of participating centers approved the studies and participants were informed of the research's purpose.

499 COVID-19 patients were included in statistical analysis. To evaluate the accuracy of ROX and PROX index in predicting negative outcome (defined as intubation or death), receiver operating characteristic (ROC) curves were used.

For the 499 patients treated with noninvasive ventilatory support outside the ICUs, 489 (98%) patients were treated with helmet CPAP and Venturi mask (VM) was used in 10 (2%) patients. In all these patients, CPAP was delivered through free-flow system with a helmet and a PEEP valve with a median set PEEP of 10 cmH_2O [IQR, 10–12.5] and a median FiO_2 of 0.6 [IQR, 0.5–0.8]. We assigned a PEEP level of 1 cmH_2O to patients treated with Venturi Mask not to modify the other variables included in the PROX index. Thereby in these patients, ROX and PROX indexes assume the same value.

Median SpO_2 and RR were 97% [IQR 94–99] and 24 breaths per minute [IQR 20–28], respectively. A negative outcome was described in 200 patients (40%), as

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Table 1 Accuracy (area under the curve—AUC), cut - off, sensitivity and specificity of ROX and PROX Index in predicting NIV success or failure

Index	AUROC	95% CI	Cut-off to predict failure	Youden's index	Sensibility	Specificity	Cut-off to predict success	Youden's index	Sensibility	Specificity
ROX	0.733	0.688–0.778	5.93	0.38	0.66	0.72	6.86	0.35	0.59	0.77
PROX	0.725	0.679–0.770	0.61	0.37	0.71	0.65	0.61	0.38	0.64	0.74

they needed endotracheal intubation or they died despite non-invasive or invasive ventilatory support.

We observed that the ROX index accuracy for predicting negative outcome is similar to the one described by Colaianni-Alfonso et al. [1], as shown in Table 1. We identified 5.93 as the threshold below which the risk of treatment failure is high. Our cut off is higher compared to the one proposed in non-COVID-19 patients receiving HFNC (3.85) [2]. The threshold to identify those patients who were likely to succeed on NIV was 6.86, which is higher than the one observed in COVID-19 patients treated with HFNC (6.86 in our study vs 5.37 observed by Zucman et al. [4]). In between the two values of ROX index (5.93 and 6.86), there was a gray zone, as described by Roca et al. [2].

PROX index has not shown an increased capacity to discriminate between patients who would succeed on NIV and those who would fail compared to the ROX index, as a comparison between the AUC of the ROC and the PROX index did not reveal any difference (p value 0.484). This unexpected result may be due to several reasons. At first, the PEEP levels applied in the overall population quote were similar and this may limit the added value of PEEP in predicting NIV failure; then repeated measures of the ROX and the PROX indexes over time were not available so we could not investigate if the prognostic performance of the two indexes changes over time. Finally, the real pressure within the CPAP helmet could be higher than the set PEEP level because HEPA and HMEF filters may act as a resistor and may increase the airway pressure within the hood, as previously demonstrated by Rezoagli et al. in a bench study [5].

In conclusion, our findings once again confirm that among hypoxemic patients treated with CPAP or VM, the ROX index may help the clinician identify patients who will fail on NIV and it may be useful not to further defer intubation, when required. Further studies are needed to elucidate the real contribution of airway pressure in predicting treatment failure during noninvasive ventilation.

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Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest.

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