Continuous positive airway pressure (CPAP) offers a valid non-invasive respiratory support for patients with Coronavirus Disease 2019 (COVID-19) pneumonia [1]. CPAP treatment isn’t free from complications such as pneumothorax/pneumomediastinum, hemodynamic instability, or delirium and requires careful monitoring [1, 2]. Accordingly, timely CPAP removal appears desirable [1, 2]. Our aim was to identify weaning predictors and assess their performance in COVID-19 patients treated with helmet CPAP.

A prospective, observational, cohort study was conducted in our high dependency respiratory unit including consecutive adult patients with laboratory confirmed COVID-19 pneumonia that underwent a weaning trial from CPAP between March 2020 and February 2021 (training cohort).

Patients’ readiness to undergo a weaning trial was judged by the treating physician. A weaning trial was the reduction in support to minimal positive end-expiratory pressure (PEEP ≈ 2 cmH2O, including antiviral filters) maintaining a FiO2 ≤ 60% [1, 2]. Absence of respiratory distress and SpO2 ≥ 94% in the subsequent 30 min lead to helmet removal and oxygen supplementation with FiO2 ≤ 60%. A weaning failure was the need to restore CPAP because of respiratory distress or SpO2 < 94% in any moment beginning from the low PEEP trial and during the subsequent 12 h.

Weaning predictors were assessed before reducing PEEP, and included: (1) ROX index (SpO2/FiO2/respiratory rate (RR)) [3], (2) modified ROX index (partial pressure of oxygen (PaO2) to FiO2 ratio/RR—mROX) [3], (3) alveolar-arterial (A-a) O2 gradient, (4) Sequential Organ Failure Assessment (SOFA) score [4].

Sensitivity and specificity for different thresholds and the area under the receiver operating characteristic curve (AUROC) was calculated for all indexes. The index that best performed in the training cohort was tested in a validation cohort of patients hospitalized in two general wards of our institution. Statistical significance was a p value ≤ 0.05. Analyses were performed with IBM SPSS Statistics V.23.0 (Armonk, NY). The study (NCT04307459) was approved by the local ethical committee (17263/2020) and all patients gave written informed consent.

Seventy-four patients formed the training cohort: 61 (82.5%) succeeded and 13 (17.5%) failed the weaning trial (Table 1). At weaning trial, patients that failed had higher SOFA score, A-a O2 and RR, while PaO2/FiO2, ROX and mROX were higher in patients that succeeded weaning (Table 1). The mROX index had the best AUROC (0.830) and the value that best discriminated weaning success from failure was 8.4 mmHg/bpm (sensitivity 0.80, specificity 0.77) (Fig. 1). This threshold was tested in the validation cohort (44 patients; median age 65, 82% males) of which 32 (72.7%) succeeded and 12 (27.3%) failed weaning. The two cohorts were comparable in terms of clinical characteristics and CPAP duration before weaning. AUROC for mROX in the validation cohort was 0.828, sensitivity and positive predictive value 0.88, specificity and negative predictive value 0.67. Patients with mROX ≥ 8.4 after 5 days of CPAP had twice the probability to be free from CPAP compared with patients with mROX < 8.4 (Fig. 1).
Our data demonstrated that the mROX index, combining non-invasive surrogates of respiratory distress (RR) and gas exchange efficiency \( \text{PaO}_2/\text{FiO}_2 \), was the best predictor of weaning success from CPAP. We observed a relatively low rate of weaning failure, suggesting that weaning attempts tend to be performed...
late, and reflecting the need for objective and sensitive indicators of weaning preparedness, as for invasive mechanical ventilation [5].

Some limitations need further exploration. First, these thresholds should be tested in randomized clinical trials and compared with standard of care. Second, predictors should be sequentially measured at different time-points during zero-PEEP, to assess their performance variability during the weaning trial and unassisted breathing [2, 6].

In conclusion, the mROX threshold of 8.4 mmHg/bpm appears a sensitive and robust predictor of weaning success from helmet CPAP in patients with COVID-19.

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Authors’ contributions
D.R., S.P. and P.S. conceived the initial idea and developed the study protocol. All authors were responsible for data acquisition and elaboration and participated in the analysis and the interpretation of data. All Authors drafted,
critically revised, and gave final approval of the final version of the manuscript. P.S. takes full responsibility of the accuracy and the integrity of the results presented.

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**Availability of data and materials**
Individual patient data will be available, upon individual and specific request, to researchers whose proposed use of the data has been approved. Data will be made available request to: pierachille.santus@unimi.it. Data will be provided with investigator support, after approval and after signing a data access agreement. The use of individual patient data outside personal consultation will not be permitted.

**Declarations**

**Ethics approval and consent to participate**
The study (ClinicalTrials.gov: NCT04307459) was designed following the amended Declaration of Helsinki (2013), was approved by the local ethical committee (Comitato Etico Area I: 17263/2020) and all patients gave written informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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