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Respiratory rate-oxygenation index on the 3rd day is the best predictor of treatment failure in COVID-19 patients

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Abstract

Predictors of outcomes are essential to identifying severe COVID-19 cases and optimizing treatment and care settings. The respiratory rate-oxygenation (ROX) index, originally introduced for predicting the failure of non-invasive support in acute hypoxemic respiratory failure (AHRF), has not been extensively studied over time during hospitalization. This multicenter prospective observational study analyzed COVID-19-related AHRF patients admitted to eight Italian hospitals during the second pandemic wave. The study assessed the ROX index using receiver operator characteristic curves and areas under the curve with 95% confidence intervals to predict treatment failure, defined as endotracheal intubation (ETI) or death.

A total of 227 patients (69.2% males) were enrolled, with a median arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO_2) ratio at admission of 248 (interquartile range: 170-295). Nearly one-third (29.5%) required ETI or died during hospitalization. Those who experienced treatment failure were older (median age 70 *vs.* 61 years, p<0.001), more likely to be current or former smokers (8.5% *vs.* 6.4% and 42.4% *vs.* 25.5%, p=0.039), had a higher prevalence of cardiovascular diseases (74.6% *vs.* 46.3%, p<0.001), and had a lower PaO_2/FIO_2 ratio at presentation (median 229 *vs.* 254, p=0.014). Gender, body mass index, and other comorbidities showed no significant differences.

In patients who failed treatment, the ROX index was higher at presentation and worsened sharply by days 3 and 4. Conversely, in patients who survived without requiring ETI, the ROX index remained stable and reduced after 5-6 days. The ROX index's pre-

dictive ability improved notably by day 3 of hospitalization, with the best cut-off value identified at 8.53 (sensitivity 75%, specificity 68%). Kaplan-Meier curves indicated that a ROX index of 8.53 or lower on days 1, 2, or 3 was associated with a higher risk of treatment failure. Thus, a single ROX index assessment on day 3 is more informative than its variability over time, with values of 8.53 or lower predicting non-invasive respiratory support failure in hospitalized COVID-19 patients.

Introduction

Since the beginning of the SARS-CoV-2 pandemic, several progress has been made in preventing and managing the most severe forms of the disease. The RECOVERY trial provided evidence that treatment with dexamethasone reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support [1]. The extensive vaccination campaigns and the introduction of early therapies, as well as the reorganization of health facilities, contributed to reducing the disease burden and its pressure on hospitals and intensive care units (ICUs) [2]. However, despite these remarkable advances, the most frequent severe manifestation of COVID-19 remains interstitial pneumonia, leading to acute hypoxic respiratory failure (AHRF) in up to 20% of the cases [3,4]. The optimal management and site of care of AHRF patients with COVID-19 remain a matter of debate. On the one hand, it is necessary to avoid ICU overload. On the other hand, in patients who do not benefit from conventional oxygen therapy or non-invasive respiratory support strategies [*i.e.,* high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV)], it is crucial not to delay endotracheal intubation (ETI) [5,6].

Therefore, predictors of outcome (*i.e.,* failure of non-invasive respiratory support) are fundamental in distinguishing these patients to optimize their treatment and site of care. In this regard, the heart rate (HR), acidosis, state of consciousness, oxygenation, and respiratory rate (HACOR) score, and the respiratory rate-oxygenation (ROX) index were introduced before the COVID-19 pandemic to predict failure of non-invasive support strategies in AHRF, with HACOR specifically focusing on the first hour of treatment [5]. Despite the ROX index, the ratio of peripheral oxygen saturation (SpO_2) and fraction of inspired oxygen (FIO_2) to respiratory rate (RR) was initially validated to predict failure of HFNC in patients with severe pneumonia (*i.e.*, score <3.85 within 12 hours) [7]; some studies also validated its usefulness in patients with COVID-19 pneumonia [8].

However, it should be considered that due to the pathophysiological peculiarities of respiratory failure in COVID-19, it is important to acquire prognostic information not only related to the first hours of admission but also during the first days of hospitalization and during non-invasive respiratory support trials [9]. The purpose of this investigation was, therefore, to evaluate the predictive role of the ROX index in identifying treatment failure (*i.e.,* ETI or death) of patients hospitalized because of COVID-19 pneumonia using data on the overall hospitalization.

Materials and Methods

This multicentric, prospective, observational study was conducted in eight university-affiliated hospitals in Italy from August 2020 to August 2021. This study was approved by the Ethics Committee of the principal site in Bergamo, Italy (Comitato Etico di Bergamo, Italy. N°308/20) and by the respective Ethics Committees of the participating centers. Informed consent was obtained from all participants, and the study was conducted in compliance with the Declaration of Helsinki (2013). For critically ill patients or those unable to sign, verbal consent was given for routine clinical parameter collection. The present analysis included patients with confirmed SARS-CoV-2 infection, determined by a positive result on real-time polymerase chain reaction of oro- and nasopharyngeal swabs at the initial test and evidence of acute respiratory failure. At the time of admission to the respiratory unit, demographic data, medical history, respiratory parameters (*i.e.,* type of respiratory support, FIO_2, SpO_2, RR), HR, systemic arterial blood pressure, and body temperature were collected. Radiologic assessments and all laboratory tests were performed according to local clinical practice and based on clinical needs. Respiratory parameters were evaluated at least once a day, when feasible, two measurements were taken, one in the morning and one in the evening. Based on these data, the ROX index was calculated using the formula $(SpO_2/FIO_2)/RR$ [7]; when two measurements were available, the ROX index was expressed as the mean value. Data collection was performed until the main outcome was reached (*i.e.,* ETI or death) or the patient was discharged.

Statistical analysis

We used descriptive statistics to summarize patients' characteristics. Continuous variables were expressed as medians and interquartile ranges (IQRs) and categorical ones as counts and percentages. Patients characteristics were stratified for composite outcome (yes/no) and differences between groups were tested using the Mann-Whitney test for continuous variables and the chi-square test (or Fisher's exact test when appropriate) for categorical variables. We performed a mixed model for repeated measures (random intercept and random slope) to evaluate the ROX index trend over time and across strata of composite outcome. Receiver operator characteristic (ROC) curves of ROX index along with areas under the curve (AUC) and corresponding 95% confidence intervals (CIs) were evaluated to predict the need of ETI or death during the first week of hospitalization. However, the optimal ROX index to discriminate the composite outcome was determined considering in particular the first 3 days of hospitalization, due to the clinical relevance of this time interval for stabilization and trial of non-invasive respiratory support [10,11]. The predictive ability of the difference between the ROX index of day 3 and day 1 (Δ ROX) and of the slope of ROX index over the first three days (obtained through a linear regression model, β ROX) was evaluated by analyzing the ROC curves and AUC. To identify the best cut-off for the ROX index, we used the ROC curves and the Liu method.

We computed time to event as the time, expressed in days, between the date of hospitalization and the date of the composite outcome, and we censored the time for patients free of events at the end of the follow-up period. Kaplan-Meier (KM) curves were stratified using the ROX index at day 1, 2 and 3; the cut-off for strata was computed on the highest AUC obtained and was used for stratifying ROX index both at day 1, and at day 2, and also at day 3. Differences in KM curves between strata of ROX index were tested using the log-rank test. Using Cox proportional hazards models, we estimated the hazard ratios (HRs) of composite outcome and the corresponding 95% CIs for ROX index, separately for days 1, 2, and 3.

For all tested hypotheses, two-sided p-values of 0.05 or less were considered significant. Statistical analysis was performed using STATA Software, release 16.1 (StataCorp LP, College Station TX, USA), and was carried out at the biostatistical laboratory of the Foundation for Research at Papa Giovanni XXIII Hospital in Bergamo.

Results

A total of 227 patients were evaluated. Their median (IQR) age was 63 (53-74) years, and 69.2% were male. The baseline characteristics are presented in Table 1. The population was generally overweight, with a median body mass index (BMI) of 27.7 kg/m^2; 62.5% had never been smokers, while 7.0% and 30.5% were active and former smokers, respectively. The main comorbidities were cardiovascular diseases, type 2 diabetes mellitus, and chronic respiratory diseases (*Supplementary Table 1*). At hospital admission, arterial blood gas analysis showed a median (IQR) PaO_2/FIO_2 ratio of 248 (170-295).

Features of patients according to main outcome

Nearly one-third of the population either required intubation or died during hospitalization (n=67, 29.5%). As shown in Table 1, compared to patients who were discharged alive, patients who either died or required intubation were older (median age 70 *vs*. 61 years, p<0.001), were more frequently smokers or former smokers (8.5% *vs*. 6.4% and 42.4% *vs*. 25.5%, p=0.039) and had a higher burden of cardiovascular disease (74.6% *vs*. 46.3%, p<0.001).

Moreover, they had a lower PaO_2/FIO_2 ratio at presentation (median 229 *vs*. 254, p=0.014). There were no differences regarding gender, BMI, or other comorbidities (Table 1).

The trend of the ROX index during the first week of hospitalization, stratified by outcomes, is reported in Figure 1. As shown, the ROX index was higher already at presentation in those who survived [9.76 (6.94-13.79) *vs.* 7.19 (6.13-9.61), p<0.001]. The ROX index increased over time for no-ETI and alive patients, and, on the opposite, it was stable or slightly decreasing in patients who died or required ETI, indicating a different effect of the ROX index time trend across the composite outcome categories (p=0.0004).

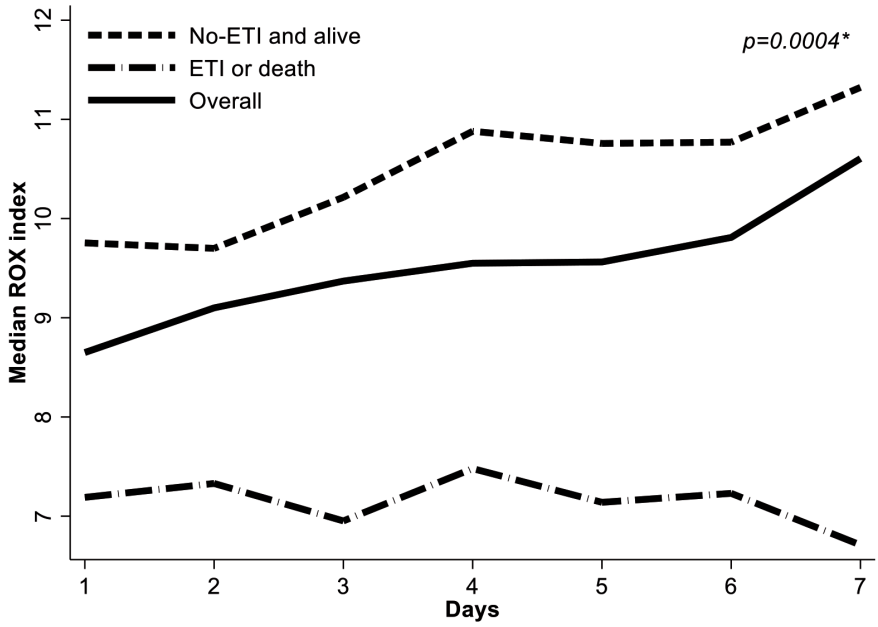
Predictive role of the respiratory rate-oxygenation index and the best cut-off

Figure 2 shows ROC curves of i) the ROX index over the first three days of hospitalization; ii) Δ ROX and iii) β ROX. The ROX index of day 3 had the best predictive ability, showing the highest

Table 1. Baseline characteristics of 227 patients according to the outcome.

		ETI or death		
	Total n=227	No n=160	Yes n=67	p
Age, median (IQR)	63 (53-74)	61 (52-71)	70 (62-80)	<0.001
≤50, n (%)	44 (20)	37 (24)	7 (11)	0.001
51-60, n (%)	51 (22)	42 (26)	9 (13)	
61-70, n (%)	58 (25)	40 (25)	18 (27)	
>70, n (%)	74 (32)	41 (25)	33 (49)	
Sex, n (%)				
Men	157 (69)	109 (68)	48 (72)	0.600
Women	70 (31)	51 (32)	19 (28)	
BMI, median (IQR)	28 (25-31)	28 (25-31)	28 (25-32)	0.740
<20.0, n (%)	2 (1)	2 (1)	0 (0)	
20.0-24.9, n (%)	35 (15)	24 (15)	11 (16)	
25.0-29.9, n (%)	102 (45)	81 (51)	21 (31)	
≥30.0, n (%)	88 (39)	53 (33)	35 (52)	
Smoke, n (%)	0.039			
No	125 (63)	96 (68)	29 (49)	
Yes	14 (7)	9 (6)	5 (9)	
Ex	61 (31)	36 (26)	25 (42)	
Immunocompromission, n (%)	12 (5)	6 (4)	6 (9)	0.110
Nefropathies, n (%)	12 (5)	6 (4)	6 (9)	0.110
Pulmonary diseases°, n (%)	28 (12)	16 (10)	12 (18)	0.098
Liver diseases, n (%)	10 (4)	6 (4)	4 (6)	0.490
Cardiovascular diseases#, n (%)	124 (55)	74 (46)	50 (75)	<0.001
Solid active neoplasia, n (%)	9 (4)	5 (3)	4 (6)	0.460
Diabetes, n (%)	38 (17)	23 (14)	15 (22)	0.140
Neurological disease, n (%)	20 (9)	11 (7)	9 (13)	0.120
Hematological disease, n (%)	11 (5)	5 (3)	6 (9)	0.062
Patologia reumatologica, n (%)	9 (4)	6 (4)	3 (5)	0.730
PaO_2/FIO_2 (at first ABG), median (IQR)	248 (170-295)	254 (189-297)	229 (120-286)	0.014
ROX day 1, median (IQR)	8.65 (6.46-12.91)	9.76 (6.94-13.79)	7.19 (6.13-9.61)	<0.001
ROX day 2, median (IQR)	9.10 (6.89-12.59)	9.70 (7.53-14.05)	7.33 (5.48-9.66)	<0.001
ROX day 3, median (IQR)	9.37 (6.94-12.43)	10.22 (8.00-13.11)	6.95 (5.82-8.75)	<0.001

ETI, endotracheal intubation; IQR, interquartile range; BMI, body mass index; PaO_2, arterial partial pressure of oxygen; FIO_2, fraction of inspired oxygen; ABG, arterial blood gas analysis; ROX, respiratory rate-oxygenation index; °includes COPD, asthma, interstitial lung diseases, bronchiectases; #includes arterial hypertension, dyslipidemia, cardiovascular diseases, (valvular diseases, hypertensive or ischemic cardiomyopathy, atrial fibrillation, arterial vasculopathy).



Median ROX [IQR]	Days						
	1	2	3	4	5	6	7
Overall							
	8.65 [6.46-12.91]	9.10 [6.89-12.59]	9.37 [6.94-12.43]	9.55 [7.54-13.47]	9.56 [7.38-13.53]	9.81 [7.78-14.18]	10.61 [7.44-14.28]
ETI or deaths							
	7.19 [6.13- 9.61]	7.33 [5.48-9.66]	6.95 [5.82-8.75]	7.48 [5.61-8.57]	7.14 [5.52-8.84]	7.23 [5.38-8.57]	6.71 [5.06-8.74]
No-ETI and alive							
	9.76 [6.94-13.79]	9.70 [7.53-14.05]	10.22 [8.0-13.11]	10.88 [8.42-14.07]	10.76 [8.19-15.02]	10.77 [8.49-15.31]	11.32 [8.47-14.97]

Figure 1. Daily median respiratory rate-oxygenation index trend, overall and stratified by outcome [endotracheal intubation (ETI) and death combined]. *p for interaction between time and outcome (ETI and death combined) obtained from a mixed model – random intercept and random slope. IQR, interquartile range; ROX, respiratory rate-oxygenation index.

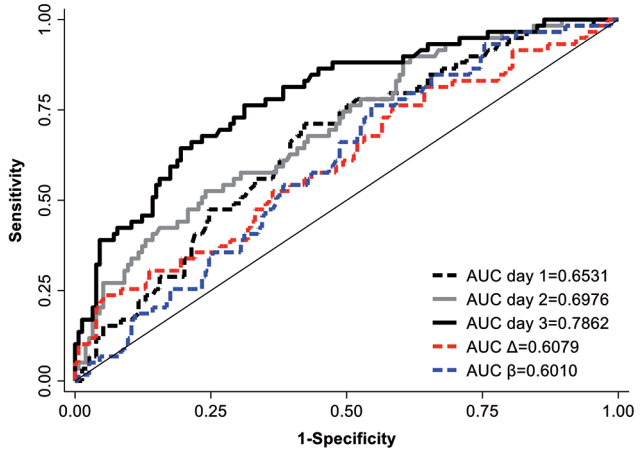


Figure 2. Receiver operator characteristic curves of respiratory rate-oxygenation (ROX) index at day 1, 2 and 3, of Δ between ROX index at day 1 and ROX index at day 3, and of regression coefficient β of ROX index at day 1 to 3 for outcome endotracheal intubation and death combined. AUC, area under the curve.

AUC (0.79, 95% CI 0.72-0.85). Supplemental analyses were performed considering ROC curves of ROX indexes over the first week, confirming the improvement in the predictive capacity of the ROX index from day 3 (*Supplementary Figure 1*).

The best cut-off of the ROX index at day 3 was 8.53 (sensitivity 75%; specificity 68%). The ROX index cut-off of 8.53 was used to investigate the ETI-free survival of the study population. KM curves show that patients with ROX index (both at day 1, and at day 2 and also at day 3) lower or equal than 8.53 have a higher risk of treatment failure (Figure 3; HR for ROX index at day 3≤8.53 was 3.6, 95% CI 2.10-6.13; HR for ROX index at day 2≤8.53 was 2.0, 95% CI 1.23-3.34; HR for ROX index at day 1≤8.53 was 2.5, 95% CI 1.46-4.16).

Discussion and Conclusions

The main results from this study can be summarized as follows: i) the median value of the ROX index is lower in COVID-19 subjects who fail treatment, already at the time of hospital admission (7.19 *vs.* 9.76); ii) a ROX index ≤8.53 is a good predictive value of

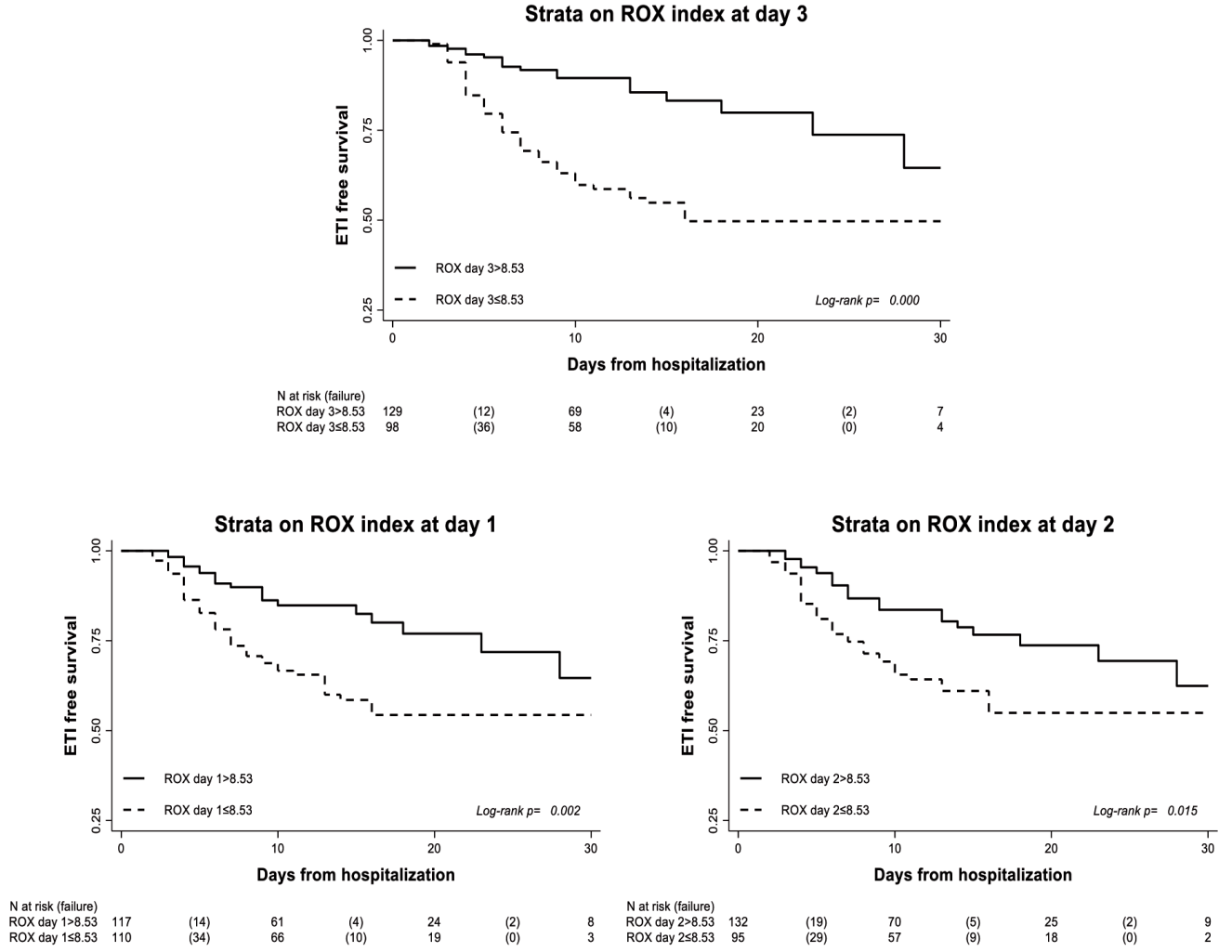


Figure 3. Kaplan-Meier curves stratified by respiratory rate-oxygenation (ROX) index (cut-off 8.53) at day 1, 2, and 3. The cut-off was computed as the best one on the ROX index on day 3. ETI, endotracheal intubation.

treatment failure at any time; iii) considering the timing of ROX index assessment, evaluation on day 3 since hospitalization is the best predictor of treatment failure; iv) single assessment of the ROX index on day 3 is more predictive than its variability over time.

Our study population is comparable to larger cohorts of patients hospitalized due to COVID-19 pneumonia, in terms of anthropometric characteristics and outcomes (*i.e.,* ETI or death) [12,13]. The main contribution of this study is given by the evaluation of the ROX index over a long period of time (*i.e.,* one week), while previous studies are generally focused on the first hours of treatment [14].

In a particular scenario, such as that of the pandemic, evaluation over a longer interval can offer advantages and better reflect what is daily clinical practice. In fact, except in conditions of instability, only a minority of COVID-19 patients are intubated in the first 24 hours [15], while most patients undergo clinical stability and possibly non-invasive respiratory support escalation during the first 48-72 hours [16,17]. Therefore, exploring the predictive role of ROX at this stage can be useful in understanding how to prioritize the intensification of patients at risk of treatment failure.

Before the COVID-19 pandemic, Roca *et al.* described the ROX index to predict the need for invasive ventilation among patients with pneumonia and acute respiratory failure treated with HFNC, showing that a ROX index ≥4.88 measured in the very first hours after HFNC therapy indicated a lower risk for treatment failure, while a ROX index ≤3.85 at 12 hours was a predictor of HFNC failure [7].

This threshold was then used by Myers *et al.* to validate ROX in a cohort of inpatients with COVID-19-related respiratory failure treated with HFNC [8]. Using a ROX threshold of 3.85, they found a positive predictive value of 59.4% (need for invasive mechanical ventilation).

However, when investigating ROX thresholds in the context of COVID-19, the results seem to be quite heterogeneous and partly differ from what has been described by Roca *et al*.

During the first pandemic wave, Zaboli *et al.* compared the ROX value obtained at triage with the medical diagnosis of acute respiratory distress syndrome (ARDS) and intubation at 72 hours [18]. Those who developed ARDS or underwent intubation had a lower average median ROX index (value of 13.1 and 15.3, respectively) compared to those who did not develop ARDS or did not require intubation (value of 25.2 and 22.2, respectively).

Similarly, Suliman *et al.* validated the ROX index on day 1 (cut-

off value ≤25.26), for predicting the risk of intubation in COVID-19 patients using the HFNC [10]. Moreover, the ROX index was investigated as a prognostic indicator among COVID-19 patients receiving CPAP, showing that values >6.32 pre-CPAP and >7.77 after 24 hours of CPAP therapy were indicative of successful weaning in >80% of the cases [19].

In accordance with our results, ROX thresholds in COVID-19 are generally higher than those of Roca *et al.* [7]. The reason behind this diversity has not been fully understood yet. However, it is possible that the heterogeneity of the study populations, which often include moderate cases, may have contributed to raising the threshold. Furthermore, relatively preserved pulmonary compliance is described during the early stages of the disease [20]. Therefore, it can be hypothesized that this accounts for a lower RR, also observed in so-called "silent hypoxia" cases, which would justify a higher ROX index [21]. Another confounding factor can be the role of shunt or blunted hypoxic pulmonary vasoconstriction in COVID-19. The administration of high FIO_2 in the case of pulmonary shunt, which is a condition of FIO_2 insensitiveness, can lead to an artifactual alteration of the respiratory exchange indices [22].

To the best of our knowledge, this is the first study to evaluate the ROX index over such a large time interval (*i.e.,* one week). The most interesting result, balancing the clinical needs with the utility of a prognostic index, was the evaluation on day 3. Indeed, the patient has generally been stabilized and has started trials of noninvasive respiratory support during the first 72 hours of hospitalization; at this point it is essential to have a prognostic tool to help us decide how to proceed. We identified a ROX index of 8.53 on day 3 (sensitivity 75%; specificity 68%) as the best cut-off for predicting failure of noninvasive respiratory support. Our cut-off limit is comparable to the threshold (ROX index = 6.64 at 24 hours) identified by Colaianni-Alfonso *et al*. in a recent study that evaluated the outcome of COVID-19 patients treated with CPAP [23], and also with the threshold (ROX index = 6.86 at 24 hours) found by Nova *et al*. when investigating the likelihood of NIV success in COVID-19 patients [24].

As already anticipated, studies that evaluate the ROX after the first 24 hours are not frequent. However, the results of Suliman *et al.* [10] during the first 3 days of hospitalization, demonstrate an increasing predictive capacity of ROX over time (ROX≤11.71 on day 3; 90% of sensitivity and 100% of specificity, AUC 0.967, p≤0.001). Regarding ROX variation over time (*i.e.,* Δ ROX), the evidence is even more limited. A recent study by Abroug *et al.* showed that the difference between ROX at 12 hours and at baseline (ICU admission) increased significantly more in the HFNC success group compared to the group failing this therapy (medians 2.7 *vs.* 0.47, respectively), finding a Δ ROX cut-off≤1.8 as the best index to predict HFNC failure (sensitivity 0.89 and specificity 0.61) [25]. We investigated the ROX variation over a wider period ($\Delta ROX_{3\text{-}1}$) and the slope of the first three ROX values (linear regression, β); however, predictive capabilities were not superior to those of ROX on day 3 (AUC $\Delta ROX_{3\text{-}1}$ 0.6079 and β 0.6010 *vs.* ROX.3 0.7862). Therefore, the threshold of 8.53 on day 3 can be interpreted as a more powerful prognostic index than the clinical trend. In other words, a patient who is improving but does not reach the expected cut-off on day 3 deserves greater clinical attention.

Our study has some limitations. Firstly, the study population was heterogeneous and had different degrees of respiratory insufficiency managed with different respiratory supports. However, we purposely enrolled a population that was representative of hospital management outside the ICU area. Therefore, the cut-offs that have been found are useful in evaluating a patient who undergoes clinical stabilization and possibly respiratory support escalation for a few days, which is the most common scenario in daily clinical practice. Secondly, studies on the ROX index generally evaluate multiple measurements of the index over the first 24 hours from the start of treatment, while in our study, we had one measure per day for the first week of hospitalization. This choice was made to investigate the predictive capacity of ROX when measured like other vital parameters in a non-intensive setting. Finally, the multicenter nature of the study may have led to differences in the intensification criteria or respiratory management of patients. However, this study considered the second and the third pandemic peak in Italy, when the treatment and respiratory support protocols were more homogeneous than in the first pandemic peak. Furthermore, the simplicity of the calculation of the ROX index can hardly lead to errors in the data collection.

In conclusion, the ROX index has shown to be a practical prognostic tool for COVID-19. A single assessment of the ROX index on day 3 since hospitalization is more informative than its variability over time, and a value ≤8.53 is predictive of failure of non-invasive respiratory support. This finding is useful in identifying patients at risk for unfavorable outcomes and guiding the decision-making process.

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Online supplementary material:

Supplementary Table 1. Detailed pneumological and cardiologic diseases according to the outcome combined.

Supplementary Figure 1. Receiver operator characteristic curves of respiratory rate-oxygenation index at day 1 to 7 for outcome endotracheal intubation and death combined.