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Ratio of Oxygen Saturation Index to Guide Management of COVID-19 Pneumonia

Coronavirus disease (COVID-19) caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged from China in December 2019, leading to a global pandemic (1). Approximately 17% of patients admitted to hospital require critical care, the majority of whom undergo mechanical ventilation (MV) for pneumonia complicated by hypoxemia (2).

High-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) are recognized treatments for hypoxemic respiratory failure caused by community-acquired pneumonia (CAP) (5–7). HFNC and CPAP may represent definitive therapy, avoiding unnecessary MV, or provide bridging respiratory support that offsets the need for immediate MV, preserving finite critical care resources. The ratio of oxygen saturation (ROX) index is used to predict the failure of HFNC in the treatment of CAP (6, 7). There are little published data describing the use of the ROX index to guide use of HFNC to treat COVID-19–associated respiratory failure; we provide further evidence to validate ROX index use in this setting (8, 9). The ROX index was developed as a simple bedside test to predict the failure of HFNC and need for MV, although patients with viral pneumonia were likely underrepresented in derivation and validation studies (6).

We undertook a retrospective observational study of individuals with laboratory-confirmed COVID-19 presenting to a single East London hospital between March 16, 2020, and April 6, 2020. Patients who received HFNC, CPAP, or MV were identified. Electronic notes review captured demographic data and clinical and respiratory parameters.

Of 393 inpatients with laboratory-confirmed COVID-19 during the study period, 255 individuals (255/393; 65.0%) were eligible for HFNC or CPAP as determined by the treating clinicians, consistent with national and local guidelines (10). A total of 108 individuals (108/255, 42.4%) received HFNC or CPAP; 69 individuals received HFNC only (63.8%), 18 received CPAP only (16.7%), and 21 received both devices (19.4%; Table 1). The majority of individuals receiving HFNC and/or CPAP experienced severe outcomes, defined as mortality or MV at 30-day follow-up (77/108; 71.3%). Most individuals who were deemed eligible for CPAP and HFNC at the time of admission were judged by treating clinicians not to require devices (147/255; 57.6%), and the majority of these individuals experienced nonsevere outcomes (138/147; 93.8%).

Table 1. Clinical variables for all patients receiving CPAP and/or HFNC

Patients	Value
Total	108
Age, yr	
Median (IQR)	62 (53–68)
Sex, *n* (%)	
M	82 (76)
Number of comorbidities	
Median (IQR)	1 (0–2)
HFNC only, *n* (%)	69 (64)
CPAP only, *n* (%)	18 (17)
CPAP and HFNC, *n* (%)	21 (19)
P/F ratio at admission (*n* = 73)	
Median (IQR)	112.5 (75.3–266.7)
ROX index at admission (*n* = 90)	
Median (IQR)	9.6 (4.3–17.0)
Do-not-intubate order at admission, *n* (%)	19 (21)
Mechanical ventilation, *n* (%)	49 (54)
Mortality, *n* (%)	33 (37)

Definition of abbreviations: CPAP = continuous positive airway pressure; HFNC = high-flow nasal cannula; IQR = interquartile range; P/F ratio = arterial oxygen pressure/fraction of inspired oxygen ratio; ROX index = ratio of oxygen saturation index.

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Table 2. Diagnostic accuracy of different respiratory variables for severe outcomes at different time points of receiving HFNC

	N	AUROC (95% CI)	Sensitivity [% *(95% CI)*]	Specificity [% *(95% CI)*]
RR ≥30 respirations/min				
0 h	88	0.64 (0.52–0.76)	36.5 (24.7–49.6)	84.0 (63.9–95.5)
2 h	79	0.58 (0.47–0.68)	35.2 (22.7–49.4)	80.0 (59.3–93.2)
12 h	57	0.53 (0.44–0.67)	28.6 (14.6–46.3)	77.3 (54.6–92.2)
ROX index <4.88				
0 h	88	0.72 (0.60–0.84)	76.2 (63.8–86.0)	60.0 (38.7–78.9)
2 h	82	0.78 (0.67–0.90)	54.4 (40.7–67.6)	88.0 (68.8–97.5)
12 h	62	0.82 (0.70–0.94)	60.0 (43.3–75.1)	86.4 (65.1–97.1)

Definition of abbreviations: AUROC = area under the receiver operating characteristics; CI = confidence interval; HFNC = high-flow nasal cannula; ROX index = ratio of oxygen saturation index; RR = respiratory rate.

For individuals receiving HFNC, median ROX indices at 2 hours (4.7 [3.7–5.9] vs. 7.0 [5.9–8.1]; $P < 0.001$) and 12 hours (4.8 [3.9–6.2] vs. 7.8 [5.2–8.7]; $P = <0.001$) after device initiation were significantly lower in the group with severe outcomes. Age- and sex-adjusted ROX indices below 4.88 at 2 (odds ratio [OR], 7.9; confidence interval [CI], 2.0–31.7) and 12 (OR, 16.3; CI, 2.8–93.6) hours after HFNC initiation increased the odds of a severe outcome. For individuals receiving HFNC, ROX index at device initiation (area under the receiver operating characteristics [AUROC], 0.72; CI, 0.60–0.84), at 2 hours (AUROC, 0.78; CI, 0.67–0.90) after device initiation, and 12 hours (AUROC, 0.82; CI, 0.70–0.94) after device initiation performed better than other respiratory variables for diagnostic accuracy of severe outcome and compared favorably with AUROC in derivation and validation studies of the ROX index for predicting intubation in patients with non–COVID-19 pneumonia (Table 2) (6, 7). A ROX index of less than 4.88 at 2 hours after HFNC initiation had the highest positive predictive value for severe outcome (91.2%; CI, 76.3–98.1%) of the respiratory variables analyzed. These results demonstrated comparable accuracy in sensitivity analyses for individuals receiving HFNC alone and individuals receiving both CPAP and HFNC (data not shown). For patients receiving HFNC, intubation-free survival was significantly reduced for individuals with a ROX index of less than 4.88 at the time of device initiation ($P = 0.0020$) and at 2 hours after device initiation ($P = 0.0154$; Figure 1). For individuals receiving only CPAP, neither ROX index at any time-point nor arterial oxygen pressure/fraction of inspired oxygen ratio at admission or at device initiation were associated with severe outcome.

Rationing of HFNC and CPAP on the basis of suitability for MV has been a strategy used widely even in high-resource settings (11). It is critical to explore the role and outcomes of HFNC and CPAP in the management of COVID-19 hypoxemic respiratory failure for patients deemed not suitable for MV. As expected, individuals who had HFNC and CPAP documented as the ceiling of care at admission (i.e., do-not-intubate orders) were older (75 years [67–81 yr] vs. 60 yr [50–66 yr]; $P > 0.001$), more frail (clinical frailty score 5 [3–5] vs. 2 [2–3], $P = 0.001$), and more comorbid (2 comorbidities [1–2] vs. 1 [0–2]; $P = 0.011$) than individuals documented for full escalation at admission. For those on HFNC, ROX indices at device initiation (2.70 [2.55–3.72]) and 2 hours after HFNC initiation (3.89 [3.15–4.17]) were significantly lower compared with ROX indices at device initiation (4.39 [3.42–5.77];, $P = 0.0059$) and at 2 hours after initiation (5.85 [4.45–7.20]; $P < 0.001$) in individuals who had MV documented as the ceiling of care at admission. Two individuals who had HFNC or CPAP documented as the ceiling of care at admission did go on to receive MV, and both

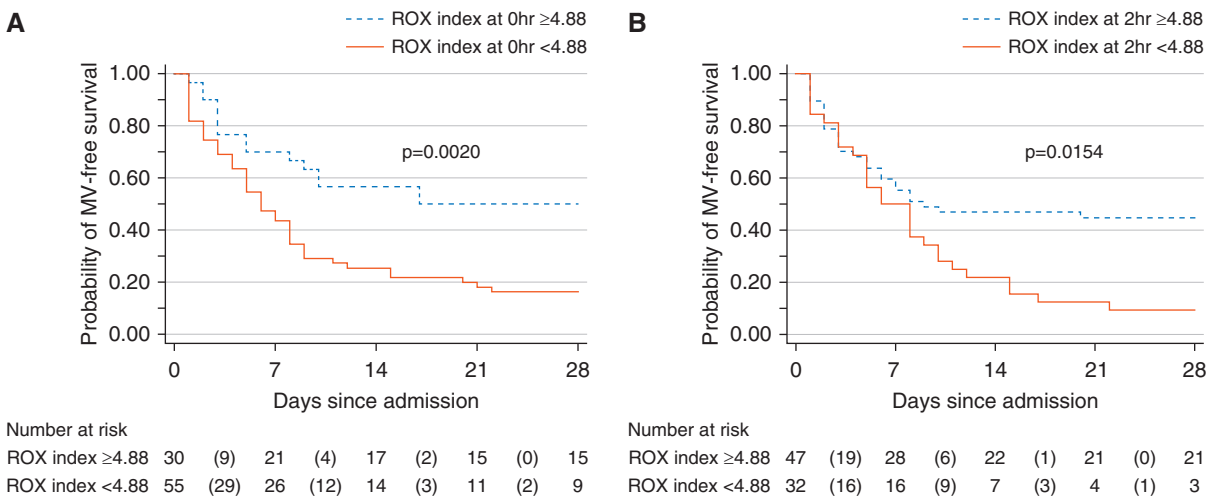

Figure 1. Kaplan-Meier plots showing probability of MV-free survival according to high (≥4.88) or low (<4.88) ROX index at high-flow nasal cannula (HFNC) initiation (0 h; *A*) or at 2 hours after HFNC initiation (*B*). MV = mechanical ventilation; ROX index = ratio of oxygen saturation index.

survived, highlighting the complex nature of decisions in the current COVID-19 landscape.

The major limitation of our study is its retrospective and single-center nature. There were a number of variables inadequately recorded in electronic notes. There are missing clinical observation data; however, these missing data are clearly highlighted in our summaries and do not prevent analysis.

Our study suggests that the ROX index is a useful predictor of failure of HFNC in COVID-19 respiratory failure to identify patients early who are likely to require MV, as suggested in earlier studies, and warrants prospective validation studies in this setting. In addition to existing literature, our data also support HFNC use guided by ROX index in individuals who have do-not-intubate orders as the ceiling of care, who have hitherto been excluded from published analyses. Further studies are required to characterize the role of the ROX index and risk stratification of HFNC failure to guide resource management and palliative care decision-making in patients deemed not suitable for MV.

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The Relation between Persistent Poor Health after COVID-19 and Respiratory Complications or Initial Disease Severity

To the Editor:

We read with interest the recent article by Townsend and colleagues that described respiratory recovery and self-reported health at the time of outpatient attendance after coronavirus disease (COVID-19) infection (1). The authors graded participants into three groups by initial severity (not requiring admission, requiring hospital admission, and requiring intensive care unit [ICU] care) by an analysis of chest radiography, a 6-minute walk test (6MWT), fatigue, frailty, subjective return to health, and some inflammatory markers (1). The authors concluded that none of the measures of persistent respiratory disease were associated with initial disease severity (1).

Because self-reported health and symptoms such as fatigue have an essentially subjective basis, the study is limited by its analysis of only a chest radiograph. This study should be complemented with computed tomography (CT) or lung function, as the follow-up protocols of scientific societies include lung function among their main evaluations (2). This takes on particular importance because, in Townsend and colleagues' study, persistent chest radiograph abnormalities attributable to COVID-19 were seen in only 4% of patients (5/115) (1), but other authors have shown approximately 70% persistence of altered CT at 3-month follow-up (3).