ROX Index to Guide Management of COVID-19 Pneumonia

Douglas L Fink[1 5], Nina R Goldman[2], James Cai[1], Karim H El-Shakankery[2], George E Sismey[2], Ankur Gupta-Wright[4 5], Charlotte X Tai[3]

[1] Department of Infectious Diseases, Whipps Cross University Hospital, London
[2] Department of Respiratory Medicine, Whipps Cross University Hospital, London
[3] Department of Anaesthetics and Critical Care, Whipps Cross University Hospital, London
4 Department of Infection and Immunity, University College London, London
5 Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London

Corresponding Author: Dr Charlotte Tai, Department of Anaesthetics & Critical Care, Whipps Cross University Hospital, Whipps Cross Road, Leytonstone, London, E11 1NR; charlotte.tai@nhs.net; +440208 539 5522, ext 5387/5825

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Coronavirus disease 2019 (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 hypoxaemia (2).

High flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) are recognised treatments for hypoxaemic 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 failure of HFNC in treatment of CAP(6,7). There are little published data describing the use of 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 failure of HFNC and need for MV, although viral pneumonia patients were likely under-represented 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 16th March and 6th April 2020. Patients were identified who received HFNC, CPAP or MV. 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). 108 individuals (108/255, 42.4%) received HFNC or CPAP: 69 individuals received HFNC only (63.8%), 18 received CPAP only

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(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 days 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 non-severe outcomes (138/147, 93.8%).

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) post device initiation, were significantly lower in the group with severe outcomes. Age and sex-adjusted ROX indices below 4.88 at 2 (OR 7.9, CI 2.0 – 31.7) and 12 (OR 16.3, CI 2.8 – 93.6) hours post HFNC initiation increased the odds of a severe outcome. For individuals receiving HFNC, ROX index at device initiation (AUROC 0.72, CI 0.60 – 0.84), at 2 hours (AUROC 0.78, CI 0.67 – 0.90) and 12 hours (AUROC 0.82, CI 0.70 – 0.94) post device initiation performed better than other respiratory variables for diagnostic accuracy of severe outcome, and compared favourably to AUROC in derivation and validation studies of ROX index for predicting intubation in patients with non-COVID-19 pneumonia (Table 2) (6,7). ROX index less than 4.88 at 2 hours post HFNC initiation had the highest positive predictive value for severe outcome (91.2%, CI 76.3% - 98.1%) of respiratory variables analysed. 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 ROX index less than 4.88 at time of device initiation (p=0.0020) and at 2 hours (p=0.0154; Figure 1). For individuals receiving only CPAP, neither ROX index at any time-point, nor P/F ratio at admission or at device initiation, were associated with severe outcome.

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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 management of COVID-19 hypoxaemic respiratory failure for patients deemed not suitable for MV. As expected, individuals who had HFNC and CPAP documented as ceiling of care at admission (i.e. do not intubate orders) were older (75 years (67-81) compared to 60 years (50-66), p>0.001), more frail (clinical frailty score 5 (3 – 5) compared to 2 (2 – 3), p=0.001) and more co-morbid (2 co-morbidities (1 – 2) compared to 1 (0 – 2), p=0.011) than individuals documented for full escalation at admission. For those on HFNC, ROX index at device initiation (2.70 (2.55 – 3.72)) and 2 hours post HFNC initiation (3.89 (3.15 – 4.17)) were significantly lower compared to ROX index at device initiation (4.39 (3.42 – 5.77), p=0.0059) and at 2 hours (5.85 (4.45 – 7.20), p<0.001) in individuals who had MV documented as ceiling of care at admission. Two individuals who had HFNC or CPAP documented as ceiling of care at admission did go on to receive MV, and both survived highlighting the complex nature of decisions in the current COVID-19 landscape.

The major limitation of our study is its retrospective and single centre 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 ceiling of care which have hitherto been excluded from published analyses. Further studies are required to characterise the role of

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ROX index and risk stratification of HFNC failure to guide resource management and palliative care decision-making in patients deemed not suitable for mechanical ventilation.

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

	Value
Total	108
Age, years **Median (IQR)**	62 (53 – 68)
Gender **Male, n (%)**	82 (76)
Number of co-morbidities **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 abbreviation: RR = respiratory rate; P/F ratio = PaO_2/FiO_2 ratio; ROX index = ratio of oxygen saturation index; HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure; RRT = renal replacement therapy; IQR = inter-quartile range.

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

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

Definition of abbreviation: RR = respiratory rate; P/F ratio = PaO_2/FiO_2 ratio; ROX index = ratio of oxygen saturation index. 95% confidence intervals are shown in parentheses.

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Figure Legend:

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

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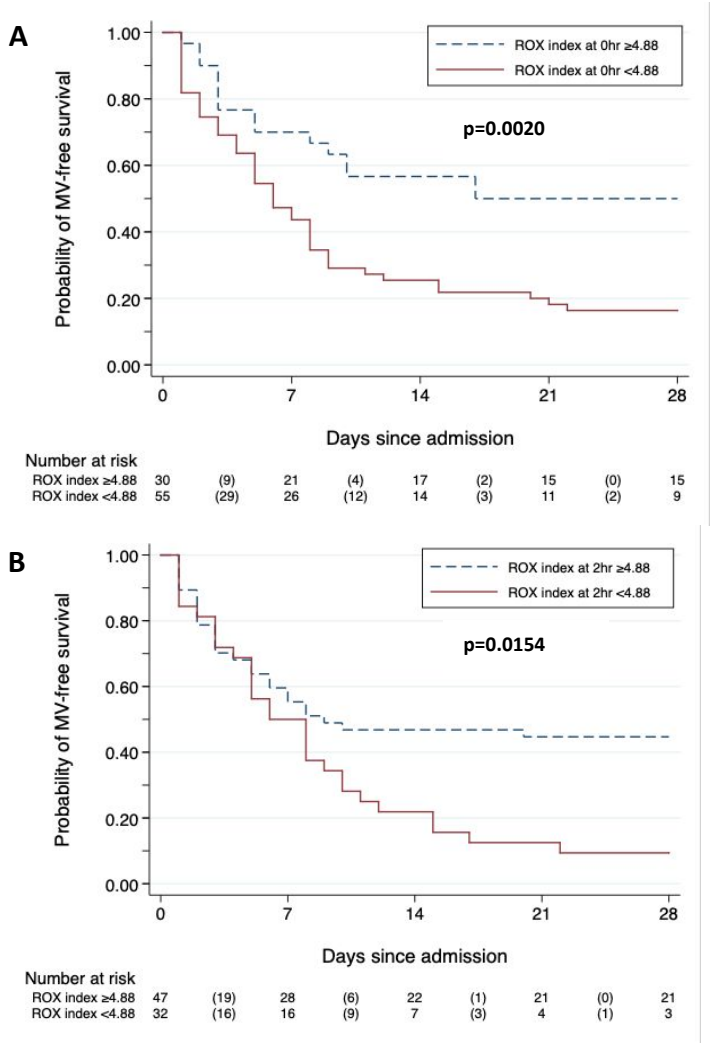

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