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Monitoring Of High-Flow Nasal Cannula For SARS-Cov-2 Severe Pneumonia: Less Is More, Better Look At Respiratory Rate

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Dear Editor,

The main clinical features of severe COVID-19 are hypoxaemia and respiratory failure [1]. Some COVID-19 patients may benefit from high-flow oxygen through nasal cannula (HFNC) [2]. However, it is critical not to delay intubation when it becomes necessary, otherwise increased mortality may be observed [3]. The "ROX index", dividing the oxygen saturation by the inspired oxygen fraction and the respiratory rate ($SpO_2/FiO_2/RR$), has been proposed to monitor patients treated with HFNC [4-5].

We conducted a monocentric prospective observational study to assess the accuracy of several parameters, including the ROX, to detect HFNC failure in the specific setting of SARS-CoV-2-related severe pneumonia**.** All the patients admitted in our intensive care unit with proven COVID-19 requiring HFNC during March and April 2020 were included. Clinical parameters were collected within the 4 hours before; and 30 minutes, 2 and 6 hours after HFNC initiation. HFNC was systematically initiated at 60 $L.min^{-1}/FiO_2$ 1. Then, FiO_2 was decreased hourly, maintaining $92\% \leq SpO_2 \leq 98\%$, down to 0.4, at which point flow was progressively reduced until weaning. "HFNC failure" was defined as the need for invasive mechanical ventilation within 7 days of HFNC onset.

Thirty patients were included (*Table S1 in the eSupplement*). Prior to HFNC, the median [IQR] RR was 30 [26-36]/min and O_2 flow was 10 [8-15] L/min. Sixteen patients met the outcome "HFNC failure" after 1 [0.9-2.5] day. The remaining 14 patients were weaned after 5 [4-7] days. Although not different before HFNC onset, RR was significantly lower at H0.5 in the "weaned" compared to the "failure" group (24 [20-24] vs. 31 [27-34]/min, p=0.004). The area under the receiver operating characteristic curve (AUROC) of RR at H0.5 was 0.81 95%CI

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[0.61-0.96] (Figure 1), with a best cut-off value at 26/min (sensitivity 75%, specificity 85%, positive likelihood ratio 4.9). RR at H2 and H6 were less informative (*Table S2*). ROX H0.5 had an AUROC of 0.78 [0.58-0.95]. Performance characteristics of ROX H0.5 using the previous published cut-off value of 4.88 [4-5] were 81% sensitivity, 38% specificity and a positive likelihood ratio of 1.3. Neither the ROX at H2 and H6, nor its changes between H0 and H0.5, H0.5-H2, and H2-H6, had better diagnostic performance than RR at H0.5 (*Tables S1 and S2*). Results for the other parameters are reported in Figure 1 and in the *eSupplement*.

The main limitations of this derivation cohort are its monocentric design and the small number of patients included. These results should be confirmed in future validation cohorts before proposing to intubate patients who are still very tachypneic as early as 30 minutes after HFNC onset. However, our results suggest that monitoring COVID-19 patients requiring HFNC with the ROX index did not add value to RR alone. This is in agreement with a possible lower diagnostic value of the ROX in viral pneumonia [4]. This may be because the ROX was mostly dependent on RR, as FiO_2 were persistently high during the first hours of HFNC [6] and as COVID-19 patients may present higher dead space due to diffuse pulmonary thrombi [7]. In addition, one-third of the patients had 100% SpO_2 despite the $92\% \leq SpO_2 \leq 98\%$ target, which may have decreased the contribution of the SpO_2/FiO_2 in the diagnostic accuracy of the ROX. Our results highlight the need for continuous monitoring of COVID-19 patients requiring HFNC, and suggested reinforcing the surveillance of patients with a RR ≥26/min half-an-hour after HFNC onset, as it may be associated with a high risk of intubation.

In conclusion, among the respiratory parameters available for monitoring COVID-19 patients treated with HFNC, using the RR is accurate and simple, thus “being most likely the right solution” according to Occam's razor.

DECLARATIONS

Funding

This work has not been funded by any external source.

Competing interests

All the authors declare that they do not have any competing interest with the current work.

Ethics approval

This work has been approved by the French Anesthesiology and Intensive Care Medicine Society (SFAR) ethical committee (IRB 00010254-2020-096).

Availability of data and material

Data are available from the corresponding author on reasonable request.

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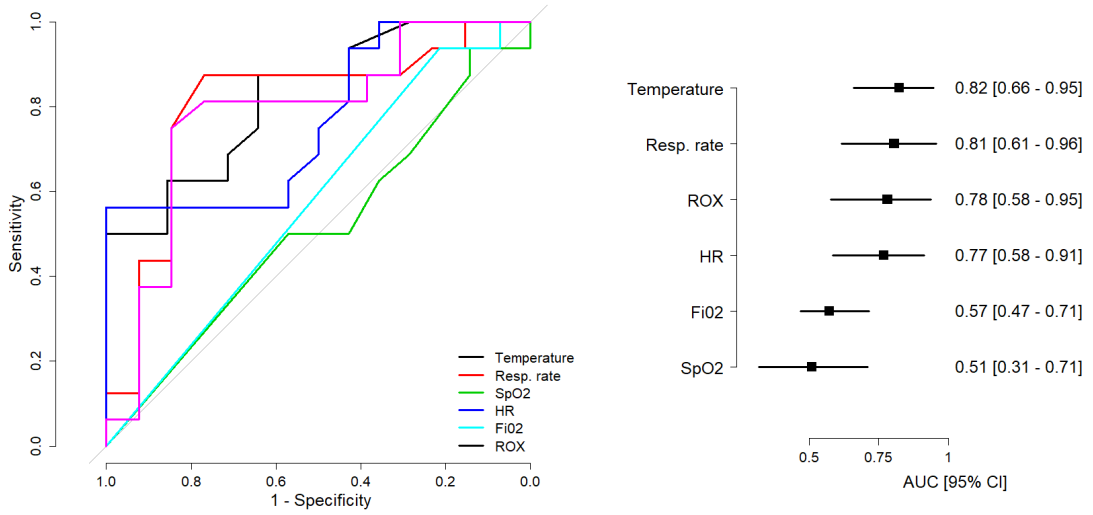
Figure 1. Receiver Operating Characteristic (ROC) curves for the principal clinical parameters for the diagnosis of high-flow nasal cannula failure



SpO_2: oxygen saturation, HR: heart rate, FiO2: inspired oxygen fraction, ROX: "Respiratory rate-Oxygenation" index

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Supplementary Table 1. Baseline characteristics of patients and evolution of their respiratory parameters over time.

	ALL PATIENTS *(n=30)*	WEANED PATIENTS *(n=14)*	HFNC FAILURE *(n=16)*	P VALUE
DEMOGRAPHIC PARAMETERS				
Age (years), *median [IQR]*	64 [59-68]	64 [57.5-72.5]	64 [59-66.3]	0.51
Sex ratio, *M/F*	21/9	11/3	10/6	0.58
BMI (kg/m²), *median [IQR]*	28.7 [25.2-31.1]	25.6 [25-28.5]	30.5 [28.4-33.1]	0.02
Hypertension, *n (%)*	16 (53%)	6 (43%)	10 (63%)	0.48
Diabetes, *n (%)*	7 (23%)	2 (14%)	5 (31%)	0.51
BASELINE CLINICAL CHARACTERISTICS				
Heart rate (/min), *median [IQR]*	86 [75-100]	85 [73-92]	98 [85-104]	0.04
Respiratory rate (/min), *median [IQR]*	30 [26-36]	28 [20-37]	30 [28-36]	0.66
SpO_2 (%), *median [IQR]*	96 [94-98]	95 [94-97]	96 [94-98]	0.93
O_2 flow (L/min), *median [IQR]*	10 [8-15]	9.5 [9-15]	10 [6.8-15]	1.00
TREATMENTS				
Antiviral agents, *n (%)*	12 (40%)	7 (50%)	5 (32%)	0.50
Corticosteroids, *n (%)*	11 (37%)	7 (50%)	4 (25%)	0.17
Anti-IL6 agents, *n (%)*	8 (27%)	6 (43%)	2 (13%)	0.14
RESPIRATORY PARAMETERS OVER TIME				
HFNC FiO_2 at H0.5, *median [IQR]*	1 [1-1]	1 [1-1]	1 [1-1]	0.26
HFNC FiO_2 at H2, *median [IQR]*	1 [0.93-1]	1 [0.83-1]	1 [1-1]	0.07
HFNC FiO_2 at H6, *median [IQR]*	1 [0.88-1]	1 [0.80-1]	1 [1-1]	0.22
RR at H0.5 (/min), *median [IQR]*	26 [22-33]	24 [20-24]	31 [27-34]	0.004
RR at H2 (/min), *median [IQR]*	29 [21-33]	25 [20-29]	33 [29-36]	0.008
RR at H6 (/min), *median [IQR]*	25 [21-31]	22 [20-27]	30 [24-34]	0.04
RR change H0-H0.5, *median [IQR]*	-1 [-7-3]	-4 [-10-4]	0 [-3-3]	0.39
RR change H0.5-H2, *median [IQR]*	1 [-2-3]	1 [-2-3]	1 [-1-4]	0.85
RR change H2-H6, *median [IQR]*	-1 [-9-2]	0 [-4-1]	-6 [-11-3]	0.69

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SpO_2 at H0.5 (%), *median [IQR]*	99 [96-100]	99 [96-100]	99 [96-100]	0.93
SpO_2 at H2 (%), *median [IQR]*	98 [96-100]	98 [96-100]	99 [96-100]	0.91
SpO_2 at H6 (%), *median [IQR]*	98 [95-100]	97 [95-100]	98 [96-100]	0.73
ROX at H0.5, *median [IQR]*	3.84 [3.13-5.00]	4.41 [4.08-6.19]	3.27 [2.92-3.79]	0.01
ROX at H2, *median [IQR]*	3.83 [2.94-4.84]	4.84 [3.84-5.44]	3.08 [2.79-3.85]	0.003
ROX at H6, *median [IQR]*	4.41 [3.42-5.43]	4.80 [4.55-6.01]	3.56 [3.00-4.25]	0.01
ROX change H0-H0.5, *median [IQR]*	-1.24 [-3.31-0.96]	0.13 [-2.54-1.07]	2.84 [0.27-3.99]	0.13
ROX change H0.5-H2, *median [IQR]*	-0.23 [-0.58-0.39]	-0.36 [-0.96-0.62]	-0.21 [-0.51-0.06]	0.98
ROX change H2-H6, *median [IQR]*	0.12 [-0.40-1.18]	0.06 [-0.87-1.08]	0.34 [-0.23-1.27]	0.55

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Supplementary Table 2. AUROC of the different clinical parameters collected

	AUROC	95% CI	P value	Best Cut-off value	P value for comparison with AUROC RR H0.5
RR H0.5	0.81	[0.61-0.96]	0.005	>26/min	-
RR H2	0.80	[0.63-0.97]	0.008	>30/min	0.90
RR H6	0.73	[0.53-0.93]	0.04	>29/min	0.35
ROX H0.5	0.78	[0.58-0.95]	0.01	<3.8	0.60
ROX H2	0.83	[0.68-0.99]	0.002	<3.4	0.80
ROX H6	0.78	[0.60-0.96]	0.01	<3.5	0.97
HR H0.5	0.77	[0.58-0.91]	0.01	>92/min	0.71
HR H2	0.80	[0,65-0,99]	0.008	>91/min	0.87
HR H6	0.55	[0,34-0,77]	0.63	>91/min	0.01
Higher temperature in the 24h after HFNC onset	0.82	[0.66-0.95]	0.003	>38.9°C	0.86

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SUPPLEMENTARY METHODS

COVID-19 pneumonia was defined as a positive result of the RT-PCR SARS-CoV-2 performed on a nasal swab with bilateral pneumonia on chest X-ray; and/or as a typical radiologic pattern on the thoracic tomodensitometry during the pandemic period as assessed by a senior radiologist + typical clinical signs of COVID-19. Along these lines, 26 patients among the 30 had a positive SARS-CoV-2 RT-PCR, while the 4 remaining patients had typical clinical presentation and evolution including cough and anosmia or aguesia with a typical radiological pattern on chest tomodensitometry.

HFNC was indicated jointly by the attending ward physician and the senior intensivist from our ICU based on an oxygen requirement above 6 L/min with a respiratory rate >20/min, and/or a rapid worsening of the clinical status despite conventional oxygen therapy (+ 4L/min O2 and/or +10/min RR over the last 6 hours).

HFNC was delivered using a high flow air-oxygen blender and the Optiflow® system (MR810 heated humidified, RT202 delivery tubing, and RT051 nasal cannula, Fisher&Paykel®).

Statistical analyses were performed using non-parametric tests with GraphPad Prism8® and R statistical software.

SUPPLEMENTARY RESULTS

In addition to the baseline characteristic of patients presented in the Supplementary Table 1, all patients had at least one major symptom of COVID-19, and were admitted into the ICU in median [IQR] 12.5 [8-14] days after the onset of symptoms. Among them 23 (77%) had cough,

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18 (60%) had fever and 8 (27%) had anosmia and/or agueusia, without any difference regarding outcome groups.

In addition to clinical data, biological data at inclusion showed a high level of inflammation (CRP 174 [88-239] mg/L; LDH 776 [567-931] UI/L; fibrinogen 7.7 [6.1-8.7] g/L) and a lymphocytopenia (800 [585-1205] G/L). There was no significant difference among all the biological data between the outcome groups, except for a higher CRP in the "High Flow Nasal Cannula (HFNC) failure" group (222 [120-281] vs. 117 [55-205] mg/L, p=0.024).

Patients were treated with antiviral agents and corticosteroids in 40% of cases, without any significant difference between the "HFNC success" and "failure" groups. Anti-IL6 agents (i.e. tocilizumab and sarilumab) were used in 6/14 (43%) and 2/16 (13%) patients in the HFNC "success" and "failure" groups, respectively (p=0.14). Awake pronation was used in 2 patients, for only a few dozen minutes for one patient with HFNC failure, and in prolonged and repeated sessions for the other with a favorable outcome.

According to our protocol, HFNC was initiated with a FiO_2 of 1 [1-1], without any difference between groups. FiO_2 remained high over the first 6 hours after HFNC onset, with a non-significant decrease between H0.5 and H6 (from 1 [1-1] to 1 [0.88-1] – p=0.10). At H6, the FiO_2 were 1 [0.8-1] vs. 1 [1-1] in the "HFNC success" and "failure" groups, respectively (p=0.22).

Although not different before HFNC onset (28 [20-37] vs. 30 [28-36]/min in the success and failure groups, respectively – p=0.66), RR decreased and became lower in the HFNC success than in the HFNC failure group at H0.5 (24 [20-24] vs. 31 [27-34] – p=0.004), H2 (25 [20-29]

vs. 33 [29-36] – p=0.008) and H6 (22 [20-27] vs. 30 [24-34] – p=0.04). The area under the receiver operating characteristic curve (AUROC) of RR at H0.5 to predict HFNC failure was 0.81 95%CI [0.61-0.96] (p=0.005, best cut-off value 26/min, *Supplementary Table S2*). AUROC of RR at H2 (0.80 [0.63-0.97] – p=0.008) was similar to that of RR at H0.5, while AUROC of RR at H6 was slightly lower (0.73 [0.53-0.93] – p=0.04).

ROX in the HFNC success group was significantly lower than in the failure group at H0.5 (4.41 [4.08-6.19] vs. 3.27 [2.92-3.79] – p=0.01), H2 (4.84 [3.84-5.44] vs. 3.08 [2.79-3.85] – p=0.003) and H6 (4.80 [4.55-6.01] vs. 3.56 [3.00-4.25] – p=0.01). However, the AUROC of the ROX to predict HFNC failure was not superior to that of RR alone at H0.5 (0.78 [0.58-0.95]), H2 (0.83 [0.68-0.99]) and H6 (0.78 [0.60-0.96]). ROX changes between H0 and H0.5, H0.5 and H2, and H2 and H6 were not different between the HFNC success and failure groups (supplementary Table S1) and were of lower interest than ROX or RR alone.