Expanding the utility of the ROX index among patients with acute hypoxemic respiratory failure

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Abstract

Background
Delaying intubation in patients who fail high-flow nasal cannula (HFNC) may result in increased mortality. The ROX index has been validated to predict HFNC failure among pneumonia patients with acute hypoxemic respiratory failure (AHRF), but little information is available for non-pneumonia causes. In this study, we validate the ROX index among AHRF patients due to both pneumonia or non-pneumonia causes, focusing on early prediction.

Methods
This was a retrospective observational study in eight Singapore intensive care units from 1 January 2015 to 30 September 2017. All patients >18 years who were treated with HFNC for AHRF were eligible and recruited. Clinical parameters and arterial blood gas values at HFNC initiation and one hour were recorded. HFNC failure was defined as requiring intubation post-HFNC initiation.

Results
HFNC was used in 483 patients with 185 (38.3%) failing HFNC. Among pneumonia patients, the ROX index was most discriminatory in pneumonia patients one hour after HFNC
initiation [AUC 0.71 (95% CI 0.64–0.79)], with a threshold value of <6.06 at one hour predicting HFNC failure (sensitivity 51%, specificity 80%, positive predictive value 61%, negative predictive value 73%). The discriminatory power remained moderate among pneumonia patients upon HFNC initiation [AUC 0.65 (95% CI 0.57–0.72)], non-pneumonia patients at HFNC initiation [AUC 0.62 (95% CI 0.55–0.69)] and one hour later [AUC 0.63 (95% CI 0.56–0.70)].

**Conclusion**
The ROX index demonstrated moderate discriminatory power among patients with either pneumonia or non-pneumonia-related AHRF at HFNC initiation and one hour later.

**Introduction**
High-flow nasal cannula therapy (HFNC) provides many benefits to critically ill patients, including reduced work of breathing, reliable oxygen delivery at higher concentrations and enhanced secretion clearance [1–3]. HFNC has gained popularity [4–6] since the landmark FLORALI study for acute hypoxemic respiratory failure (AHRF) among patients with pneumonia [7]. Many centres have broadened indications beyond pneumonia [8,9], using it in pulmonary hemorrhage [10], acute exacerbation of chronic obstructive pulmonary disease (COPD) [9,11–13] and heart failure [14]. Its use has extended beyond the intensive care unit (ICU) to the emergency department (ED), where the aetiology of the hypoxemic respiratory failure may not yet be ascertained [9,14].

Although HFNC has been used among AHRF patients with non-pneumonia indications, existing evidence for HFNC use has been mainly among pneumonia patients. The FLORALI study demonstrated lower intubation rates among pneumonia patients with PaO$_2$/FiO$_2$ ratio (PF ratio) less than 200 mmHg when compared to those receiving conventional oxygen therapy (COT) and non-invasive ventilation (NIV), although up to 40% still required intubation [7]. Prior studies among non-pneumonia patients focused mainly on physiological parameters [8–14], with the failure rate remaining largely unknown. Understanding HFNC failure rates is important, because mortality may be increased if intubation is delayed [15].

In this respect, Roca and colleagues developed the ROX index to help predict HFNC failure in patients with pneumonia [16,17]. The ROX index is the ratio of SpO$_2$/FiO$_2$ (SF ratio) to respiratory rate. It has excellent specificity (98–99%) for predicting HFNC failure at various time points of 2 (<2.85), 6 (<3.47) and 12 hours (<3.85), albeit at the expense of low sensitivity [17]. Physicians have subsequently attempted to improve the ROX index [18] and explore its utility as a predictor of weaning failure [19]. Current evidence supporting the use of the ROX index is limited to pneumonia patients mainly at later time points, limiting its utility.

Understanding the performance of the ROX index at earlier time points, would enhance prediction of HFNC failure, facilitating earlier intubation and potentially averting increased mortality risks. In this study, we aimed to expand the utility of the ROX index as a tool for predicting HFNC failure by validating its use at earlier time points among both pneumonia and non-pneumonia patients. We hypothesized that the ROX index could discriminate patients likely to experience HFNC failure at earlier time points in both pneumonia and non-pneumonia AHRF.
Methods

Study design

We conducted a retrospective observational multi-center study in all public hospital intensive care units (ICU) in Singapore of patients using HFNC for AHRF from 1 January 2015 to 30 September 2017. The National Healthcare Group Domain-Specific Review Board approved the study with a waiver of informed consent due to the non-interventional study design (DSRB 2017/00900).

Patients

Patients were included if they were older than 18 years and treated with HFNC for AHRF. Patients with concomitant hypercapnia were also included. Patients were excluded if they had do-not-intubate orders for the current AHRF episode or if HFNC was used for pre-oxygenation, post-extubation management or peri-procedural purposes. HFNC initiation was at the discretion of the primary physician.

Device description and management

HFNC was provided with one of the following devices: Optiflow device (MR850 heated humidified delivery tubing and nasal cannula; Fisher & Paykel Healthcare, Auckland, New Zealand), Bio-med device high flow air-oxygen blender with the heated humidifier (MR850, Fisher & Paykel Healthcare, Auckland, New Zealand) or the Airvo 2 device (Fisher & Paykel Healthcare, Auckland, New Zealand). Despite the different devices, all the nasal cannula interfaces were similar to the Airvo2 device, where the nasal cannula is able to deliver humidified respiratory gases up to flows of 70L/min. Physicians initiated HFNC at a minimum flow of 30L/min with FiO\textsubscript{2} of at least 30% to target a SpO\textsubscript{2} of at least 92%.

Data collection

Demographic characteristics were collected for all patients including: age, gender, ethnicity, admission source and comorbidities (diabetes, hypertension, ischemic heart disease, stroke, asthma, COPD, bronchiectasis, interstitial lung disease, liver cirrhosis and chronic kidney disease). Immunocompromised state was also determined, defined as the presence of any solid tumor, hematological malignancy, or usage of steroids (at least 0.3mg/kg/day for at least 1 month) or other immunosuppressants. Illness severity was determined from the Acute Physiology and Chronic Health Evaluation (APACHE) II score and frequency of vasopressor use.

The underlying etiology of AHRF was categorized into one of the following: (a) pneumonia, defined as the presence of respiratory symptoms with radiological evidence on chest radiograph; (b) heart failure; (c) COPD exacerbation; (d) asthma exacerbation; (e) exacerbation of interstitial lung disease; (f) HFNC use post-surgery; (g) others. In cases where multiple etiologies may account for the patient’s AHRF, the leading etiology was determined by the primary physician.

HFNC failure was defined as requiring intubation after HFNC initiation. However, since this was a retrospective observational study, and none of the participating ICUs used a specific protocol to determine intubation decisions among the HFNC patients, the intubation decision occurred at the discretion of the managing physician. ICU mortality, hospital mortality, ICU length-of-stay and hospital length-of-stay were also collected.

As mentioned, the ROX index is the ratio of the SF ratio to respiratory rate. In order to compute the ROX index as defined by Roca and colleagues [17], the following parameters...
were collected immediately prior to HFNC initiation, after one hour and in the event of HFNC failure, at the point of intubation: SpO\(_2\) (%), FiO\(_2\) (%), respiratory rate (breaths/min), flow rate (L/min) and arterial partial pressure of carbon dioxide (PaCO\(_2\), in mmHg) [16,17].

Statistical analysis

Univariate comparisons of proportions, means and medians were performed using the Chi-square test, Student t, and Wilcoxon rank-sum tests respectively. Separate subgroup analyses were performed for both pneumonia and non-pneumonia populations. We assessed the discrimination of the ROX index using receiving operating characteristic (ROC) curves. Using parameters at HFNC initiation and one hour later, the Youden index method was used to determine the optimal cut-point of the ROX index for HFNC failure. Statistical significance was taken as a two-tailed P<0.05, and analyses were performed with Stata 15.0 (College Station, TX).

Results

Patient characteristics and outcomes

Eight ICUs participated in this study. 483 patients required HFNC for AHRF, of whom 45 patients also had concomitant hypercapnia. 263 patients (54%) had a primary diagnosis of pneumonia (Fig 1). The remaining patients who received HFNC had cardiovascular conditions (n = 58), utilized HFNC post-surgery (n = 57), and for non-pulmonary acute respiratory distress syndrome (n = 25), COPD (n = 14), interstitial lung disease (n = 7) or asthma exacerbations (n = 1). 185 patients (38.3%) failed HFNC. Baseline demographics were mostly similar

![Fig 1. Enrolment and outcomes.](https://doi.org/10.1371/journal.pone.0261234.g001)
between both patients with pneumonia and non-pneumonia conditions. Patients with non-pneumonia conditions were more likely to have ischemic heart disease and less likely to be admitted from the operating theatre (Table 1).

### Performance of the ROX index among pneumonia patients only

Out of 263 patients with pneumonia, 101 (38.4%) required intubation. Among those who failed HFNC, they were more tachypneic [27 (23–33) breaths/min vs 24 (20–28) breaths/min, \( p = 0.006 \)], tachycardic [106 (89–118) beats/min vs 95 (83–107) beats/min, \( p < 0.001 \)] and were initiated on HFNC at lower SF ratio [176 (97–243) vs 208 (115–257), \( p = 0.006 \)] immediately prior to HFNC initiation. None of the other non-respiratory parameters were predictive of

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**Table 1. Baseline characteristics of patients with hypoxemic respiratory failure.**

|                                | All patients (n = 483) | Patients with pneumonia (n = 263) | Patients with non-pneumonia conditions (n = 220) | \( p \) value |
|--------------------------------|------------------------|----------------------------------|-----------------------------------------------|-------------|
| Median Age, (Years)            | 64 (55–74)             | 65 (55–74)                       | 63 (56–73)                                    | 0.689       |
| Male                           | 345 (71.4%)            | 190 (72.2%)                      | 155 (70.5%)                                   | 0.687       |
| Median BMI (kg/m\(^2\))        | 22.9 (20.0–26.7)       | 22.8 (19.6–26.0)                 | 22.9 (21.2–27.0)                              | 0.074       |
| Median APACHE II               | 19 (13–25)             | 19 (13–25)                       | 20 (13–25)                                    | 0.633       |
| Vasopressor use                | 94 (19.5%)             | 43 (16.4%)                       | 51 (23.2%)                                    | 0.065       |
| **Smoking status**             |                        |                                  |                                               |             |
| Smoker                         | 86 (17.8%)             | 40 (15.2%)                       | 46 (20.9%)                                    | 0.271       |
| Ex-smoker                      | 335 (69.4%)            | 188 (71.5%)                      | 147 (66.8%)                                   |             |
| Non-smoker                     | 62 (12.8%)             | 35 (13.3%)                       | 27 (12.3%)                                    |             |
| **Admission source**           |                        |                                  |                                               |             |
| Emergency Department           | 207 (42.9%)            | 83 (37.7%)                       | 124 (47.2%)                                   | <0.001*     |
| General Ward                   | 233 (48.2%)            | 102 (46.4%)                      | 131 (49.8%)                                   |             |
| Operating Theatre              | 43 (8.9%)              | 35 (15.9%)                       | 8 (3.0%)                                      |             |
| **Comorbidities**              |                        |                                  |                                               |             |
| Hypertension                   | 282 (58.4%)            | 149 (56.6%)                      | 133 (60.5%)                                   | 0.406       |
| Diabetes                       | 181 (37.5%)            | 100 (38.0%)                      | 81 (36.8%)                                    | 0.850       |
| Immunosuppression              | 133 (27.5%)            | 67 (25.5%)                       | 66 (30.0%)                                    | 0.306       |
| Chronic kidney disease         | 104 (21.5%)            | 59 (22.4%)                       | 45 (20.5%)                                    | 0.657       |
| Ischemic Heart Disease         | 103 (21.3%)            | 40 (15.2%)                       | 63 (28.6%)                                    | 0.001*      |
| COPD                           | 34 (7.0%)              | 14 (5.3%)                        | 20 (9.1%)                                     | 0.112       |
| Stroke                         | 32 (6.6%)              | 17 (6.5%)                        | 15 (6.8%)                                     | 1.000       |
| Asthma                         | 28 (5.8%)              | 12 (4.6%)                        | 16 (7.3%)                                     | 0.242       |
| Liver cirrhosis                | 15 (3.1%)              | 7 (2.7%)                         | 8 (3.6%)                                      | 0.604       |
| Bronchiectasis                 | 11 (2.3%)              | 8 (3.0%)                         | 3 (1.4%)                                      | 0.359       |
| Interstitial lung disease      | 9 (1.9%)               | 4 (1.5%)                         | 5 (2.3%)                                      | 0.738       |
| **Outcomes**                   |                        |                                  |                                               |             |
| Median duration of HFNC use (Hrs) | 23 (9–49)             | 23 (10–53)                       | 21 (9–46)                                     | 0.614       |
| Median ICU length of stay (days) | 6 (3–10)              | 6 (3–11)                         | 6 (3–10)                                      | 0.503       |
| Median hospital length of stay (days) | 18 (10–35)         | 15 (9–29)                        | 21 (11–41)                                    | 0.023*      |
| ICU mortality                  | 71 (14.7%)             | 47 (17.9%)                       | 24 (10.9%)                                    | 0.039*      |
| Hospital mortality             | 120 (24.8%)            | 78 (29.7%)                       | 42 (19.1%)                                    | 0.008*      |

* represents those parameters that are statistically significant.

**BMI = Body mass index, APACHE II = Acute Physiology and Chronic Health Evaluation II, ED = Emergency Department, COPD = Chronic obstructive pulmonary disease.

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HFNC failure. These differences persisted one hour after HFNC initiation (Table 2). Those who failed HFNC already required higher FiO\textsubscript{2} one hour of HFNC initiation [60% (50%-70%) vs 50% (40%-60%), p<0.001]. These results remained consistent when patients with concomitant hypercapnia were excluded (S1 Table).

### Table 2. Parameters of patients with hypoxemic respiratory failure at various stages of HFNC use.

| Parameters | Patients with pneumonia only (n = 263) | Patients with non-pneumonia conditions only (n = 220) |
|------------|---------------------------------------|-----------------------------------------------|
|            | Patients who failed HFNC and required intubation (n = 101) | Patients who used HFNC successfully and avoided intubation (n = 162) | p value | Patients who failed HFNC and required intubation (n = 84) | Patients who used HFNC successfully and avoided intubation (n = 136) | p value |
|            |                                      |                                               |       |                                                               |                                                               |       |
|            | Clinical and serological parameters (Median, Inter-quartile range) |                                               |       |                                                               |                                                               |       |
|            |                                      |                                               |       |                                                               |                                                               |       |
| Pre-HFNC BIPAP use (%) | 18 (17.8) | 33 (20.5) | 0.634 | 20 (23.8) | 41 (30.2) | 0.354 |
| Pre-HFNC CPAP use (%) | 11 (10.9) | 26 (16.2) | 0.277 | 13 (15.5) | 23 (16.9) | 0.853 |
| Respiratory rate (breaths/min) | 27 (23–33) | 24 (20–28) | 0.006* | 25 (21–29) | 24 (19–29) | 0.417 |
| FiO\textsubscript{2} (%) | 50 (40–100) | 50 (36–80) | 0.007* | 45 (36–50) | 40 (35–50) | 0.516 |
| SpO\textsubscript{2} (%) | 95 (92–98) | 95 (92–98) | 0.553 | 95 (91–98) | 95 (91–97) | 0.775 |
| SF ratio | 176 (97–243) | 208 (115–257) | 0.006* | 200 (170–257) | 238 (185–277) | 0.035* |
| ROX index | 5.93 (3.93–8.97) | 8.18 (5.00–11.55) | <0.001* | 7.92 (6.06–10.78) | 10.02 (7.23–13.04) | 0.021* |
| PaCO\textsubscript{2} (mmHg) | 33 (29–40) | 34 (30–37) | 0.356 | 35 (31–39) | 35 (29–39) | 0.426 |
| Serum HCO\textsubscript{3} (mmol/l) | 22.2 (20.0–26.4) | 22.5 (19.3–26.0) | 0.150 | 22.5 (19.2–26.6) | 23.0 (20.2–26.2) | 0.064 |
| pH | 7.44 (7.41–7.48) | 7.43 (7.39–7.48) | 0.208 | 7.43 (7.37–7.48) | 7.41 (7.38–7.46) | 0.617 |
| Heart rate (bpm) | 106 (89–118) | 95 (83–107) | <0.001* | 96 (83–113) | 100 (81–114) | 0.960 |
| Systolic blood pressure (mmHg) | 136 (115–157) | 128 (111–153) | 0.256 | 121 (101–141) | 126 (107–145) | 0.351 |
| Diastolic blood pressure (mmHg) | 75 (63–85) | 72 (61–83) | 0.661 | 66 (52–78) | 70 (60–81) | 0.072 |
| Median GCS | 15 (15–15) | 15 (15–15) | 0.175 | 15 (14–15) | 15 (15–15) | 0.436 |
| 1 hr after HFNC administered |                                      |                                               |       |                                                               |                                                               |       |
| Respiratory rate (breaths/min) | 26 (23–31) | 23 (19–30) | 0.004* | 24 (19–28) | 22 (18–27) | 0.338 |
| Flow (L/min) | 50 (50–60) | 50 (40–50) | 0.605 | 50 (45–60) | 50 (40–60) | 0.783 |
| FiO\textsubscript{2} (%) | 60 (50–70) | 50 (40–60) | <0.001* | 50 (40–60) | 40 (35–50) | 0.001* |
| SpO\textsubscript{2} (%) | 96 (93–98) | 96 (94–99) | 0.436 | 95 (93–97) | 96 (94–98) | 0.877 |
| SF ratio | 164 (134–194) | 190 (158–232) | <0.001* | 196 (165–240) | 240 (186–271) | 0.001* |
| ROX index | 6.74 (4.53–8.70) | 8.56 (6.74–11.19) | <0.001* | 8.03 (6.58–11.06) | 10.35 (7.48–14.00) | 0.001* |
| PaCO\textsubscript{2} (mmHg) | 33 (29–38) | 34 (29–38) | 0.823 | 34 (30–39) | 33 (28–38) | 0.814 |
| Serum HCO\textsubscript{3} (mmol/l) | 23.1 (20.0–27.0) | 23.0 (20.7–26.0) | 0.223 | 23.8 (20.3–26.0) | 22.0 (20.0–24.5) | 0.259 |
| pH | 7.45 (7.40–7.49) | 7.44 (7.40–7.47) | 0.616 | 7.44 (7.40–7.50) | 7.44 (7.40–7.47) | 0.440 |
| Heart rate (bpm) | 102 (86–118) | 92 (82–103) | <0.001* | 98 (83–112) | 96 (81–106) | 0.289 |
| Systolic blood pressure (mmHg) | 133 (116–150) | 129 (111–149) | 0.727 | 119 (107–137) | 120 (106–137) | 0.916 |
| Diastolic blood pressure (mmHg) | 69 (61–81) | 69 (60–79) | 0.809 | 68 (55–77) | 67 (59–77) | 0.564 |
| Median GCS | 15 (15–15) | 15 (15–15) | 0.682 | 15 (14–15) | 15 (15–15) | 0.389 |

* represents those parameters that are statistically significant.

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The ROX index was more discriminatory among pneumonia patients one-hour post-initiation [AUC 0.71 (95% CI 0.64–0.79)] as compared to upon HFNC initiation [AUC 0.65 (0.57–0.72)]. A ROX index <4.58 at HFNC initiation and <6.06 one-hour post-initiation predicted HFNC failure with 80% specificity (Table 3 and S1Fig).

### Performance of the ROX index among non-pneumonia patients only

Among 220 patients with non-pneumonia AHRF, 84 (38.2%) failed HFNC. Patients who failed HFNC predominantly had lower median SF ratio compared to those who used HFNC successfully [200 (170–257) vs 238 (185–277), p = 0.035] immediately prior to HFNC initiation. Unlike pneumonia patients, patients who failed HFNC were not more tachypneic or tachycardic. One-hour after HFNC administration, these clinical characteristics still persisted. Again, higher FiO\textsubscript{2} was already required among those who failed HFNC [50% (40%-60%) vs 40% (35%-50%), p = 0.001] (Table 2). These results remained consistent when patients with concomitant hypercapnia were excluded (S1 Table).

The ROX index still showed moderate discrimination at HFNC initiation [AUC 0.62 (95% CI 0.57–0.68)] and one hour later [AUC 0.65 (0.60–0.71)]. Correspondingly, a ROX
Discussion

Among AHRF patients with pneumonia, the ROX index demonstrated moderate discriminatory power to predict HFNC failure, with greater discrimination one-hour post-initiation compared to when HFNC was initiated. In a similar fashion, the ROX index was also validated as moderately discriminating among non-pneumonia AHRF patients at similar time points. Roca and colleagues originally validated the ROX index in patients with pneumonia [16,17]. However, at least 20% of all ICU patients with AHRF suffer from non-pneumonia-related conditions [21]. In some subgroups such as immunocompromised patients, the etiology of AHRF is even more varied [20,22–25], and in ED, HFNC may be initiated before the underlying etiology of AHRF is established [9]. Since delayed intubation can increase mortality regardless of the cause of AHRF [7], it is important to understand the performance of the ROX index among patients with non-pneumonia-related conditions. Currently, there are few studies investigating HFNC use among this population and they mainly focused on demonstrating physiological benefits [2,7,26–28]. In contrast, our study focused on understanding the performance of the ROX index among a more diverse HFNC population.

In addition, as the ROX index was originally validated at 2, 6 and 12 hours [16,17], we explored its ability to discriminate patients likely to fail HFNC at earlier time points. This would facilitate early pre-emptive intubation before further deterioration has occurred [15]. We demonstrated that at one-hour post-HFNC initiation, the AUROC of the ROX index for predicting HFNC failure was 0.71 and 0.63 for pneumonia and non-pneumonia patients respectively. Therefore, we have shown that the ROX index calculated immediately prior to HFNC initiation and one-hour post-initiation can help identify those likely to fail. Since HFNC is increasingly initiated while patients are still in ED, predicting HFNC failure at earlier time points can guide the development of practical workflows for close monitoring, especially in settings where staffing resources for close patient monitoring is scarce, or transfer time from ED to ICU is prolonged. Identifying patients most likely to fail HFNC may facilitate earlier intubation decisions and increase safety during patient transport [29].

It is important to highlight that the ROX index is a screening tool with only moderate discriminatory power. In the original study, Roca and colleagues report AUROC values at 2 hours of 0.679, 6 hours of 0.703 and 12 hours of 0.752 [17]. We report similar values in our study (Table 3). To maximize the screening tool potential of the ROX index, the values adopted favoured higher specificity and negative predictive values, so as to reduce false positives. To illustrate, a ROX index of <6.06 (sensitivity 51%, specificity 80%) among pneumonia patients one-hour post-HFNC initiation would have led to an additional 46 patients being intubated. Importantly, our study also highlights the importance of serial measurements of the ROX index given the dynamic evolution of the disease course among these patients. Depending on the study population, the exact ROX index value predicting HFNC failure may differ. This is illustrated with the studies by Roca and Goh separately depicting different values at the same time points at 2 (<2.85 vs <6.55), 6 (<3.47 vs <6.60) and 12 (<3.85 vs <6.55) hours [17,18].

Our study has several strengths. It is a practical real-world evaluation. Our study population was large, from multiple centers and included AHRF patients with multiple etiologies. This allowed us to validate the ROX index at earlier time points and among non-pneumonia patients. To date, this is the largest study population investigating HFNC failure among non-pneumonia patients. However, we acknowledge several limitations in our study. Firstly, it was conducted retrospectively, and in the absence of a standardized protocol, we were unable to
study the ROX index at other time points, in particular at later time points, which could be a subject for future studies. Secondly, the lack of a standardized protocol for HFNC practice could have led to biases from individual physician practice patterns and thresholds for determining HFNC failure. Thirdly, as with all retrospective studies, some missing data is inevitable, with the majority related to arterial blood gas findings one-hour post-HFNC initiation. Other studies have already established that these parameters do not predict HFNC failure [16,18,19]. Otherwise, all other parameters were missing <10% of the total data, thus mitigating the bias risk (S1 Table). Fourthly, determination of HFNC failure was clinically-driven rather than protocolized, and some variation of HFNC failure thresholds existed across centers (S3 and S4 Tables). Importantly, our HFNC failure rate of 38.3% is also similar to that of the FLORALI study [7]. Finally, in the absence of randomization, we are unable to account for the effect of unmeasured variables that may affect the ROX index.

**Conclusion**

There is moderate discriminatory power of the ROX index to predict HFNC failure among both pneumonia and non-pneumonia patients with AHRF upon HFNC initiation and one-hour post-initiation.

**Supporting information**

S1 Fig. ROC Curves of the ROX index prior and one-hour post-HFNC initiation among both pneumonia and non-pneumonia patients.

(PPTX)

S1 Table. Parameters of patients with only hypoxemic respiratory failure at various stages of HFNC use.

(DOCX)

S2 Table. Missing data upon HFNC initiation and one-hour post HFNC initiation.

(DOCX)

S3 Table. Median values of parameters of patients at each site who failed HFNC at the point of intubation.

(DOCX)

S4 Table. Parameters of patients with pneumonia and non-pneumonia conditions who failed HFNC at the point of intubation.

(DOCX)

S1 Dataset. Key to dataset.

(XLSX)

S2 Dataset. Minimal anonymized data set.

(XLSX)

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References

1. Goligher EC, Slutsky AS. Not Just Oxygen? Mechanisms of Benefit from High-Flow Nasal Cannula in Hypoxic Respiratory Failure. *Am J Respir Crit Care Med*. 2017; 195:1128–1130. https://doi.org/10.1164/rcrm.201701-0006ED PMID: 28459344

2. Mauri T, Turini C, Eronia N, et al. Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure. *Am J Respir Crit Care Med*. 2017; 195:1207–1215. https://doi.org/10.1164/rcrm.201605-0916OC PMID: 27997805

3. Ricard JD, Roca O, Lerniale V, et al. Use of nasal high-flow oxygen during acute respiratory failure. *Intensive Care Med*. 2020; 46:2238–2247. https://doi.org/10.1007/s00134-020-06228-7 PMID: 32901374

4. Messika J, Ben Ahmed K, Gaudry S, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: a 1-year observational study. *Respir Care* 2015; 60:162–169. https://doi.org/10.4187/respcare.03423 PMID: 25371400

5. Gaunt KA, Spilman SK, Halub ME, Jackson JA, Lamb KD, Sahr SM. High-flow nasal cannula in a mixed adult ICU. *Respir Care* 2015; 60:1383–1389. https://doi.org/10.4187/respcare.04016 PMID: 26060320

6. Hyun Cho W, Ju Yeo H, Hoon Yoon S, et al. High-flow nasal cannula therapy for acute hypoxemic respiratory failure in adults: a retrospective analysis. *Intern Med* 2015; 54:2307–2313. https://doi.org/10.2169/internalmedicine.54.4266 PMID: 26370853
7. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxic respiratory failure. *N Engl J Med* 2015; 372:2185–2196. https://doi.org/10.1056/NEJMoa1503326 PMID: 25981908

8. Sotello D, Orellana-Barrios M, Rivas AM, Nugent K. High flow nasal cannulas for oxygenation: an audit of its use in a tertiary hospital. *Am J Med Sci* 2015; 350:308–312. https://doi.org/10.1097/MAJ.0000000000000557 PMID: 26351777

9. Jones PG, Kamona S, Doran O, Sawtell F, Wilsher M. Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: the HOT-ER study. *Respir Care* 2016; 61:291–299. https://doi.org/10.4187/respcare.04252 PMID: 26577199

10. Schwabauer N, Bjorn B, Blumenstock G, et al. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation. *BMC Anesthesiology* 2014; 14:66. https://doi.org/10.1186/1471-2253-14-66 PMID: 25110463

11. Sztrymf B, Messika J, Bertrand F, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. *Intensive Care Med* 2011; 37: 1780–1786. https://doi.org/10.1007/s00134-011-2354-6 PMID: 21946925

12. Braunlich J, Kholer M, Wirtz H. Nasal high flow improves ventilation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2016; 11:1077–1085. https://doi.org/10.2147/COPD.S104616 PMID: 27307723

13. Fraser JF, Spooner AJ, Drumster KR, et al. Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. *Thorax* 2016; 71:759–761. https://doi.org/10.1136/thoraxjnl-2015-207962 PMID: 27015801

14. Makdee O, Monsomboon A, Surabengjawong U, et al. High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. *Ann Emerg Med* 2017; 70:465–472. https://doi.org/10.1016/j.annemergmed.2017.03.028 PMID: 28601264

15. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula may delay intubation and increase mortality. *Intensive Care Med* 2015; 41:623–632. https://doi.org/10.1007/s00134-015-3693-5 PMID: 25891263

16. Roca O, Messika J, Caralt B, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxic respiratory failure: the utility of the ROX index. *J Crit Care* 2016; 35:200–205. https://doi.org/10.1016/j.jcrc.2016.05.022 PMID: 27481769

17. Roca O, Caralt B, Messika J, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high flow therapy. *Am J Respir Crit Care Med* 2019; 199:1368–1376. https://doi.org/10.1016/j.ajrccm.2019.03.028 PMID: 30576221

18. Goh KJ, Chai HZ, Ong TH, et al. Early prediction of high flow nasal cannula therapy outcomes using a modified ROX index incorporating heart rate. *Journal of Intensive Care* 2020; 8:11. https://doi.org/10.1186/s40560-020-00458-z PMID: 32587703

19. Rodriguez M, Thille AW, Boissier F, et al. Predictors of successful separation from high-flow nasal oxygen therapy in patients with acute respiratory failure: a retrospective monocentre study. *Ann Intensive Care* 2019; 9:101. https://doi.org/10.1186/s13613-019-0578-8 PMID: 31519996

20. Azoulay E, Lemiale V, Mokart D, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure—the HiGH randomized clinical trial. *JAMA* 2018; 320:2099–2107. https://doi.org/10.1001/jama.2018.14262 PMID: 30357270

21. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800. https://doi.org/10.1001/jama.2016.2993337

22. Lemiale V, Resche-Rigon M, Mokart D, et al. High-flow nasal cannula oxygenation in immunocompromised patients with acute hypoxic respiratory failure: a Groupe de Recherche respiratoire en reanimation onco-hematologique study. *Crit Care Med* 2017; 45:e274–e280. https://doi.org/10.1097/CCM.0000000000002085 PMID: 27655324

23. Frat JP, Ragot S, Girault C, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *Lancet Respir Med* 2016; 4:646–652. https://doi.org/10.1016/S2213-2600(16)30093-5 PMID: 27245914

24. Azoulay E, Mokart D, Kouatchet A, Demoule A, Lemiale V. Acute respiratory failure in immunocompromised adults. *Lancet Respir Med* 2018; 7:173–186. https://doi.org/10.1016/S2213-2600(18)30345-X PMID: 30529232

25. Azoulay E, Pickkers P, Soares M, et al. Acute hypoxic respiratory failure in immunocompromised patients; the Efraim multinational prospective cohort study. *Intensive Care Med* 2017; 43:1808–1819. https://doi.org/10.1007/s00134-017-4947-1 PMID: 28948369
26. Pilcher J, Eastlake L, Richards M, et al. Physiological effects of titrated oxygen via nasal high-flow canulae in COPD exacerbations: a randomized controlled cross-over trial. *Respirology* 2017; 22:1149–1155. https://doi.org/10.1111/resp.13050 PMID: 28470831

27. Braunlich J, Kohler M, Wirtz H. Nasal high-flow improves ventilation in patients with COPD. *Int J COPD* 2016; 11:1077–1085. https://doi.org/10.2147/COPD.S104616 PMID: 27307723

28. Braunlich J, Byer D, Mai D, et al. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. *Respiration* 2013; 85:319–325. https://doi.org/10.1159/000342027 PMID: 23128844

29. Liew MF, Siow WT, Yau YW, See KC. Safe patient transport for COVID-19. *Crit Care* 2020; 24:94. https://doi.org/10.1186/s13054-020-2828-4 PMID: 32183864