Predictors of Nasal High-flow Humidified Oxygen Therapy Failure: A Narrative Review

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Abstract: High-flow nasal cannula oxygen therapy (HFNC) is a widely used non-invasive respiratory support for patients with mild acute hypoxemic respiratory failure (AHRF). Early identification of HFNC failure risk can facilitate timely intervention and avoid poor outcomes. Currently, there is a paucity of reliable predicators to predict HFNC failure. Roca et al. introduced the ROX index as a predictor of intubation risk in pneumonia patients undergoing HFNC. Subsequently, various modified predictors have been proposed to address limitations of the ROX index; however, their predictive performance remained under investigation and had not yet been universally validated. In this study, we investigated and analyzed the development and current application status of known HFNC failure predictors to provide ideas and recommendations on further relevant researches.

***Keywords*:** high-flow nasal cannula oxygen therapy, acute hypoxemic respiratory failure, risk prediction, the ROX index

1. Introduction

High flow nasal cannula (HFNC) is a novel type of oxygen therapy that delivers heated and humidified oxygen flow to the nasal cavity with nasal cannula. Compared with conventional oxygen therapy (COT), HFNC provide a gas flow up to 60L/min and FiO_2 up to 100% without nasal mucosal irritation and dryness and bleeding. It has advantages of reducing dead space ventilation, lowering the resistance of nasopharyngeal airway in physiological mechanisms and improving oxygenation by generating end-expiratory positive pressure[1].

2. The application of ROX index

HFNC played an important role in respiratory support since Waugh et al.[2] found HFNC devices could maintain better humidification of airflow than COT. Kim et al.[3]suggested that HFNC had advantage in certain perioperative situations, such as preoxygenation, anesthesia induction, and awake endotracheal intubation, and might replace endotracheal intubation techniques during laryngeal microsurgery. The FLORALI trial[4] confirmed a similar intubation rate of HFNC to COT and non-invasive ventilation (NIV) in acute hypoxemic respiratory failure (AHRF) patients. For AHRF or non-surgical extubation patients with low risk, HFNC is preferable[5-7]. Moreover, Yang et al.[8] encouraged its use in patients with chronic obstructive pulmonary disease (COPD), which was conditionally approved by guidelines[5].

HFNC failure is often defined as requirement of mechanical ventilation (MV), deterioration of condition, hemodynamic instability or death before MV, respectively[9]. Roca et al.[10] proposed "ROX Index", as the ratio of SpO_2/FiO_2 to respiratory rate (RR), to predict the risk of HFNC failure. Their next prospective study[11] suggested that ROX index showed good predictive efficiency after the initiation of HFNC and a ROX index over 4.88 was associated with lower intubation rate.

3. The limitation of ROX index

The primary limitation is the efficiency. To our knowledge, the AUCs of ROX index in many recent studies, shown in Table 1, were seldom over 0.8, some were even close to 0.5. Roca et al.[11] concluded an area under the receiver operating characteristic curve (AUC) of 0.801 at 24h of HFNC, which might be the highest among studies to our knowledge. The predictive efficiency varied among patients with specific types of respiratory failure. In immunocompromised patients, as Lemiale et al.[12] discovered, the AUC is not satisfying. Schaeffer et al.[13] found that the AUC of ROX index to predict HFNC/NIV failure was about 0.72 in patients with COPD. Li A et al.[14] found its AUC between pneumonia and non-pneumonia patients was similar, but only up to 0.71 at most. A low and heterogeneous value of efficiency caused the distrust of ROX index.

Secondary, its undetermined reference range. Roca et al.[11] gave a cutoff value of 4.88 to determine the risk of intubation. But Deana et al.[15] found that the ROX index reached above 14 in HFNC treated patients after esophageal surgery, far higher than 4.88. This may result from a good respiratory function of patients for elective surgery. Same

predicament was shown in patients with pneumonia as well. A meta-analysis[16] suggested the cutoff values in most studies were centered between 4.5 and 6.0, with a median of 5.3.

These limitations may associate with diversity and severity of diseases, cooperation of patients, and attitude of physicians towards switching respiratory support which was significantly correlated with HFNC failure[17]. The presence of extra-pulmonary organ failures would also increase the risk of HFNC failure[18]. The formula to calculate ROX index itself is also doubtful, as Karim et al.[19]stressed that the non-linear relationship between SpO_2/FiO_2 and PaO_2/FiO_2 and the different levels of hemoglobin may cause errors. The misestimation of actual flow, that is physiologically affected by air leak, stenosis, secretions, patients' cooperation, etc., could cause an unreliable result. Hopefully, Montecchia et al. invented a flow monitoring device that might change this situation[20].

Table 1. Studies of HFNC in adult patients involving the ROX index or its variants or other predictors.

Study	Study design	Population	Predictors	Toal cases	Definition of Outcomes
Grünewaldt, 2024[21]	Monocenter retrospective observational study	CAP or COVID-19 pneumonia	ROX, q-SOFA, CRB65	245	HFNC failure: need for IMV or death before intubation
Calle-Peña, 2024[22]	Monocenter retrospective observational study	COVID-19 diagnosed	ROX, SpO_2/FiO_2, WBS	156	HFNC failure: the presence of at least 1 criterion: hemodynamic instability, shock, vasopressor requirements, PaO_2/FiO_2 <100, $PaCO_2$ > 40, increased work of breathing with paradoxical breathing, and persistent RR ≥ 30/min
Wang, 2024[23]	Monocenter retrospective observational study	COVID-19	ROX, mROX	57	HFNC failure: intubation after 2 h HFNC
Kang, 2024[24]	Monocenter retrospective study	HFNC in ED	ROX, ROX-HR	97	HFNC failure: intubation in ED
Liu, 2024[25]	Multicenter prospective cohort study	HFNC patients	ROX, GPT-3.5, GPT-4.0	71	HFNC failure: intubation within 48 h
Castro-Sayat, 2024[26]	Monocenter prospective cohort study	ARF due to COVID-19	ROX, LUS	101	HFNC failure: the need to switch to CPAP devices to maintain oxygenation
Ruchiwit, 2024[27]	Monocenter retrospective observational study	COVID-19 pneumonia	ROX, CROX, dCROX	106	HFNC weaning success: sustain spontaneous breathing after separation from HFNC without any invasive or noninvasive ventilatory support for ≥ 48 h or death
Okano, 2024[28]	Multicenter retrospective observational study	COVID-19 diagnosed	ROX, HACOR	300	HFNC failure: intubation or death within 7 days
Ruchiwit, 2024[29]	Monocenter retrospective observational study	COVID-19 pneumonia	ROX, HROX, delta-HR	164	HFNC weaning success: sustain spontaneous breathing after separation from HFNC without any invasive or non-invasive ventilatory support for ≥ 48 h or death
Michel, 2024[30]	Retrospective cohort study	COVID-19 with AHRF	ROX, DEOx	373	HFNC failure: intubation based on AMCI guidelines
Liu, 2023[31]	Monocenter retrospective observational study	AHRF	ROX, PaO_2/FiO_2	142	HFNC failure: No improvement symptoms and change to NIV or IMV
Ruangsomboon, 2023[32]	Multicenter retrospective study	COVID-19 patients in EDs	ROX, SpO_2/FiO_2, ROX-HR	173	HFNC success: no requirement of IMV at HFNC termination
Yu, 2023[33]	Monocenter retrospective study	COVID-19 with AHRF	ROX, VICE	69	HFNC failure: requirement of IMV after HFNC use
Praphruetkit, 2023[34]	Monocenter prospective observational study	AHRF patients in ED	ROX, HACOR	75	HFNC success: no intolerance or escalation towards IMV or NIV within 48 h
Bruna, 2023[35]	Monocenter prospective cohort study	respiratory failure secondary to SARS-CoV-2 pneumonia	ROX, excursion and diaphragmatic contraction speed (diaphragmatic excursion/ inspiratory time) by ultrasound	41	HFNC failure: need for intubation or death
Abroug, 2023[36]	Monocenter observational study	COVID-19–related ARF	ROX, delta-ROX	213	HFNC failure: need for intubation
Karim, 2022[37]	Monocenter prospective observational pilot study	COVID-19 requiring intensive care management and HFNC	ROX, mROX	27	HFNC failure: need for either NIV (Bi-level) or IMV
Kansal, 2022[38]	Monocenter retrospective study	ARF	ROX, POX-HR, delta POX-HR	111	HFNC failure: need to escalate to intubation or NIV within 48 h of HFNC application for respiratory causes only

Study	Study design	Population	Predictors	Toal cases	Definition of Outcomes
Ibarra-Estrada, 2022[39]	Multicenter prospective observational study	COVID-19-induced AHRF treated with APP	ROX, LUS, SpO_2/FiO_2	71	Treatment failure: patient intubated
Zablockis, 2022[40]	Monocenter prospective observational study	COVID-19-related AHRF	ROX, CCI	124	HFNC failure: requirement of IMV or death during HFNC therapy
Li Z, 2022[41]	Monocenter retrospective cohort study	AHRF	ROX, mROX, ROX-HR, mROX-HR	75	HFNC success: improvement of respiratory status without requiring intubation for MV during ICU stay
kim, 2022[42]	Multicenter retrospective study	COVID-19 diagnosed	ROX, SpO_2/FiO_2	133	HFNC failure: need for subsequent intubation despite HFNC application
Valencia, 2021[43]	Comparative Study	COVID-19 pneumonia patients in ED	ROX, HACOR	245	HFNC failure: need for mechanical ventilation onset and death associated with COVID-19 pneumonia
Li Z, 2021[44]	Monocenter prospective study	AHRF	ROX, EIT-based parameters (GI, CoV, I:E)	46	HFNC failure: intubation within 48 h after HFNC
Liu Taotao, 2021[45]	Database retrospective cohort study	Adult patients with COPD and mild hypercapnia	ROX, HR/SpO_2	153 (Only 37 for HFNC)	Outcome: intubation rate at 48 h and 28 d
Hu, 2020[46]	Multicenter retrospective observational study	severe COVID-19	ROX, PaO_2/FiO_2, SpO_2/FiO_2	105	HFNC failure: need for NIV or IMV and/or death while on HFNC support
Goh, 2020[47]	Prospective observational cohort study	AHRF and HFNC after planned extubation	ROX, ROX-HR	145	HFNC failure: need for mechanical ventilation

Abbreviation: AHRF: Acute hypoxemic respiratory failure; AMCI: Asociacion de Medicina Critica y Cuidado Intesivo de Colombia; APP: Awake prone positioning; ARF: Acute respiratory failure; CAP: Community-acquired pneumonia; CCI: Charlson Comorbidity Index; DEOx: quantitative measurement of oxygen debt; COPD: chronic obstructive pulmonary disease; ED: Emergency Department; EIT: Electrical impedance tomography; HFNC: High-flow nasal cannula; HR: Heart rate; IMV: Invasive mechanical ventilation; LUS: lung ultrasound score; NIV: Non-invasive ventilation; RR: Respiratory rate; SAPS-2:Simplified Acute Physiology Score II; VICE: Ventilation in COVID-19 estimation; WBS: Work of breathing scale. Definition of indexes: ROX: The ratio of SpO_2/FiO_2 to RR; mROX: Modified ROX (PaO_2/FiO_2 to RR); POX-HR: The ratio of PaO_2/FiO_2 to (RR×HR), same as mROX-HR; ROX-HR: The ratio of SpO_2/FiO_2 to (RR×HR); mROX-HR: The ratio of PsO_2/FiO_2 to (RR×HR).

4. Modification and comparison of predictors

Many possible predictors were under investigation now in HFNC, as shown in Table 1. Valencia et al.[43] firstly studied the use of HACOR score proposed by Duan et al.[48] in COVID-19 patients treated with HFNC. Li Z et al.[41] modified the ROX index by replacing SpO_2 with PaO_2. Goh et al.[47] created "ROX-HR" by integrating heart rate with the ROX index based on the theory that tachycardia might reflect declining cardiac reserve function through enhanced sympathetic nervous system and maladaptation. Carroll et al.[49] put airflow into account and created Fox index ($Flow \times FiO_2/SpO_2$). Chen et al.[50] proposed VOX index, which was defined as the ratio of SpO_2/FiO_2 to tidal volume (TV), according to the finding that TV changed along with respiratory drive but RR increased only when respiratory drive was three to four times higher than normal[51]. However, how to measure TV for HFNC treatment is still a question. However, the sample sizes were small and the populations of most studies were restricted to patients infected with COVID-19, which led to a situation with no predictors that are attractive enough and highly recommended.

To enhance the quality of evaluation, the use of chest X-ray, ultrasound, electrical impedance tomography (EIT) and even artificial intelligence has become a trend[25, 39, 52]. Nonetheless, the use of these techniques is not always affordable in resource-limited regions, which goes against the original intention of the guideline who brought in HFNC therapy and the conception of SpO_2/FiO_2[7]. Therefore, the studies on modified forms of ROX index or other novel or existing predictors composed of common clinical variables are still mainstream.

5. Conclusion

Predicting HFNC failure is critical as delayed intubation will influence prognosis. The ROX index has been put into practice somewhere but is still controversial. Imaging features may helpful, but still costly and time consuming. An improved predictor can effectively balance medical costs and clinical performance; hence it is both promising and essential to make better study design and perform subgroup analysis to find a more feasible predictor with higher sensitivity, specificity and more general reference range.

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