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Comparison of ROX index with modified indices incorporating heart rate, flow rate, and PaO_2/FiO_2 ratio for early prediction of outcomes among patients initiated on post-extubation high-flow nasal cannula therapy

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Abstract

Background Incorporation of heart rate, flow rate, and PaO_2/FIO_2 (PF) ratio to ROX index has been postulated to better predict high-flow nasal cannula (HFNC) usage outcomes in post-extubation setting. Therefore, we aimed to compare ROX index with new modified indices to predict HFNC outcomes in the post-extubation setting.

Methods This single-centre 6-year retrospective study included subjects initiated on HFNC post-extubation. The modified indices (ROX-HR, ROX-HR-Flow and POX-HR-Flow) incorporated HFNC flow rate, heart rate and substituted PF ratio for SF ratio. Evaluation was performed using AUROC and cut-offs assessed for prediction of HFNC outcomes.

Results Eighty-one subjects were initiated on HFNC post-extubation, of whom 67 patients (82.7%) had HFNC success. ROX-HR-Flow at 2 h post-HFNC initiation demonstrated the best prediction accuracy (AUROC 0.854, 95% CI 0.756–0.952). A ROX-HR-Flow > 12.25 at 2 h post-HFNC initiation was significantly associated with a lower risk of HFNC failure (Sensitivity 77.6% and Specificity 85.7%).

Conclusions Our proposed modified index at 2 h post-HFNC initiation (ROX-HR-Flow), may facilitate early and accurate prediction of HFNC outcomes compared to ROX index among subjects initiated on HFNC in the post-extubation setting.

Keywords HFNC, HFNC failure, Adult ICU, Post-extubation, Respiratory failure, Indices

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Introduction

Extubation failure requiring re-intubation is seen in around 10–15% of patient who undergo planned extubation [1–3]. Patients who require re-intubation following extubation failure have poorer prognosis with longer hospital stay and mortality as high as 30–40% [4].

Among patients at high risk of extubation failure, high-flow nasal cannula (HFNC) is being increasingly utilized

to decrease the risk of re-intubation in the post-extubation setting [5, 6]. However, the rate of re-intubation despite post-extubation HFNC application is still around 9.5%–18.1% [7–10]. Since delayed intubation has been associated with poorer outcomes, early recognition of patients likely to fail HFNC can be immensely helpful in clinical decision-making [11]. The common risk factors associated with HFNC failure when used in the post-extubation setting are hypoxia, hypercapnia, presence of stroke, longer hospital stay, longer duration of mechanical ventilation [7, 8].

To facilitate easy prediction of HFNC failure, indices based on physiological parameters have been developed. ROX index ([oxygen saturation/FiO_2]/respiratory rate) has been developed and validated to have good predictive ability for HFNC outcomes in acute respiratory failure (ARF) [12–18]. A recent meta-analysis by Prakash et al. suggested that ROX index has good discriminating power for prediction of HFNC failure in COVID-19 patients with acute hypoxemic respiratory failure [19].

While ROX is a convenient bedside index, only few studies have analysed the ROX index in the post-extubation setting [9, 13, 20]. Additionally, previous studies suggest that ROX index can be improvised by incorporating other commonly available clinical variables, namely heart rate (HR), flow rate of HFNC and substitution of PaO_2/FiO_2 (PF) ratio instead SpO_2/ FiO_2 (SF) ratio [13, 21–23].

Tachycardia after HFNC therapy initiation has been found to be associated with HFNC failure [24–26]. Tachycardia is likely to be surrogate for the sympathetic drive due to increased work of breathing. Studies have shown that incorporating HR with the ROX index (ROX-HR) performed better than ROX index alone among the patients initiated on the HFNC for ARF [13, 22, 23] as well as preventive use in post-extubation setting [13].

Higher flow rate of HFNC is associated with better oxygenation as well as reduction in respiratory rate [27]. Since the flow rate of HFNC affects the main variables of ROX, it would be expected to affect the ROX index as well. This was shown in a study done by Mauri et al. where they found that increasing set flow rate from 30 to 60 l/min led to a small but significant increase of the ROX index (10.21 [7.15–13.33] vs. 11.14 [8.81–13.93], $p=0.003$), corresponding to an increase of 7 percentage [21].

The SpO_2 used in ROX index is known to be influenced by body temperature, pigmentation of skin, hypoperfusion, acid–base status and haemoglobin levels which results in discrepancy between SpO_2 and actual oxygen levels in blood [28, 29].. Studies have shown that the relationship of SF ratio and the PF ratio is not linear [30, 31]. Moreover, factors affecting oxygen dissociation curve, e.g., temperature, PH, $PaCO_2$ are commonly deranged in critically ill patients and thereby further affecting the relationship between SpO_2 and PaO_2 [32]. Recent studies have demonstrated that a modified ROX index incorporating PF ratio performed better than ROX index alone, among ARF patients initiated on HFNC [22, 23]. However, there are no published studies evaluating HFNC outcome prediction in the post-extubation setting by incorporating PF ratio.

Therefore, we aimed to compare ROX with three modified indices—ROX-HR (incorporating heart rate), ROX-HR-Flow (incorporating heart rate and flow) and POX-HR-Flow (substituting PF ratio for SF ratio and incorporating heart rate and flow) for early prediction of outcome among patients initiated on post-extubation HFNC.

Methods

Study design and patient population

The study was conducted in a mixed adult intensive care unit (ICU) of a tertiary care public hospital in Singapore. We included all adult patients admitted to the ICU who were initiated on HFNC over a six-year period from January 1, 2016 to 31 Dec 31, 2021. For subjects with multiple ICU admissions and HFNC usage within one hospitalization, only the first HFNC episode post-extubation was included. Data were collected retrospectively from the electronic medical records. The National Healthcare Group (NHG) Domain-Specific Review Board (DSRB) approved the study with a waiver of informed consent due to the non-interventional retrospective study design (NHG DSRB reference number—2020/01167).

Patients were included if they were older than 18 years and had been initiated on HFNC post-extubation. Decision to start post-extubation HFNC was as per the clinical judgement of the trained intensivists, based on usual risk factors for re-intubation, e.g., elderly, and obese patients, moderate-to-severe chronic obstructive pulmonary disease (COPD), multiple comorbidities, higher severity of illness at ICU admission, inability to deal with respiratory secretions, and longer duration of mechanical ventilation [1–3]. Patients were excluded if there was an urgent need to intubate within 2 h after HFNC initiation because we considered that such patients were likely to be too sick to be trialled on HFNC. We also excluded patients with a 'do not resuscitate or do not intubate' order. Among patients who were started on HFNC post-extubation, for this study we also excluded the patients on beta-blocker therapy or sick sinus syndrome or those who had arrhythmia. This was done as these conditions would alter the normal physiological response of change in heart rate. Heart rate is an important variable for all the 3 modified ROX indices being considered in this study.

The study ICU was always covered by trained intensive care consultants and respiratory therapists. Readiness for extubation was based on experts' clinical judgement and usual accepted criteria, including resolution of underlying pathology requiring intubation, minimal oxygenation and ventilatory requirements on pressure-support ventilation, Fio2 usually less than 40%, hemodynamic stability (low-dose vasopressors acceptable), no significant metabolic and electrolyte abnormalities to name a few [1].

Clinical management and definition of HFNC failure

Airvo 2™ (Fisher & Paykel Healthcare, Auckland, New Zealand) was used for providing HFNC therapy post-extubation. Among the patients identified for HFNC support post-extubation, HFNC was started at a minimum flow of 50 L/min (50–60 L/min) [23, 33], titrating the FiO_2 to achieve an oxygen saturation of ≥ 92% as per routine practice in our unit [23]. Usually, HFNC would be reduced to 30-40L/min once FiO_2 is stable at 30–40% and thereafter switch to standard oxygen therapy in next 6–24 h if clinically stable. Need for escalation of respiratory support to re-intubation or non-invasive ventilation (NIV) was decided by the treating clinicians based on their clinical judgement as deemed appropriate. We defined HFNC failure as escalation of respiratory support to positive pressure ventilation (mechanical ventilation or NIV) or death within 48 h of HFNC usage, post-extubation. We used 48 h as an endpoint acknowledging that a re-intubation later than 48 h may not be related to the early physiological parameters. Patients were followed up till death or hospital discharge.

Modified indices description

The modified indices considered were ROX-HR, ROX-HR-Flow, and POX-HR-Flow. The indices were calculated as follows:

1) ROX index = (SF/RR)
2) ROX-HR = [SF/(RR*HR)] * 100
3) ROX-HR-Flow = [SF/(RR*HR*Flow)] * 100 * 60
4) POX-HR-Flow = [PF/(RR*HR*Flow)] * 100 * 60.

For the ROX, ROX-HR and ROX-HR-Flow—the time intervals considered were pre-extubation (at the time when last ABG prior to extubation), at the time of HFNC initiation and post-extubation at 2 hours, 6 hours, 12 hours. For the POX-HR-Flow—the intervals considered were pre-extubation and after HFNC initiation, depending upon the timing of ABG analysis.

Statistical analysis

Categorical variables were reported as frequencies and proportions and were compared using the Chi-square test. Non-parametric data were reported as median (interquartile range, IQR) and compared using the standard median test. Youden index was used to determine the cut-offs for the indices, rounded off to the nearest 0.1 (maximize the clinical utility through the sum of sensitivity and specificity), based on the receiver operating characteristic (ROC) curves. From these cut-offs, Kaplan–Meier (KM) plots for HFNC success were determined and compared using the log-rank test. Variables that have p-value less than 0.1 were included in the multivariate Cox proportional regression analysis. Univariate and multivariate Cox proportional regression analysis was performed to evaluate various indices. Post hoc power calculation was done based on observed HFNC failure rate, setting the acceptable significance level ($\alpha = 0.05$) for 2-tailed alternative hypotheses and assigning the power of the study at 80% ($\beta = 0.2$). Area under ROC (AUROC) with internal variances was calculated.

AUROC provides a comprehensive measure of discriminative ability across all possible thresholds, which is particularly valuable in clinical settings where optimal thresholds may vary. It allows for robust comparison between different predictive models or indices, including our modified ROX indices. AUROC's threshold independence and intuitive 0.5–1.0 scale facilitate interpretation and comparison with other studies in critical care literature. Given our relatively small sample size, AUROC offers a robust measure that is less sensitive to sample size limitations. It also allows for consistent comparison across multiple time points in our study. To address AUROC's limitations in providing information about calibration or clinical utility at specific thresholds, we complemented our analysis with additional metrics such as sensitivity, specificity, and Kaplan–Meier survival analysis. Statistical difference was considered significant at $p \leq 0.05$. All statistical analyses were performed using the SPSS software (version 23.0 SPSS Inc., Chicago, Illinois, USA).

Results

A total of 134 patients received HFNC in the post-extubation setting during the 6-year study period. 53 of these patients were excluded: 3 patients had HFNC support for less than 2 h, and 21 patients had a 'do not resuscitate or intubate' order. 21 patients were on beta-blocker therapy, 1 patient had a pacemaker and 7 patients had arrhythmia. None of them were on beta-2 agonist. Remaining 81 patients were eligible for the study analysis (Fig. 1).

The baseline characteristics are presented in Table 1. Pneumonia was the most common primary diagnosis (76.5%). The median PF ratio was 243.3 (IQR 199.1–294.4). These patients had a Charlson Comorbidity

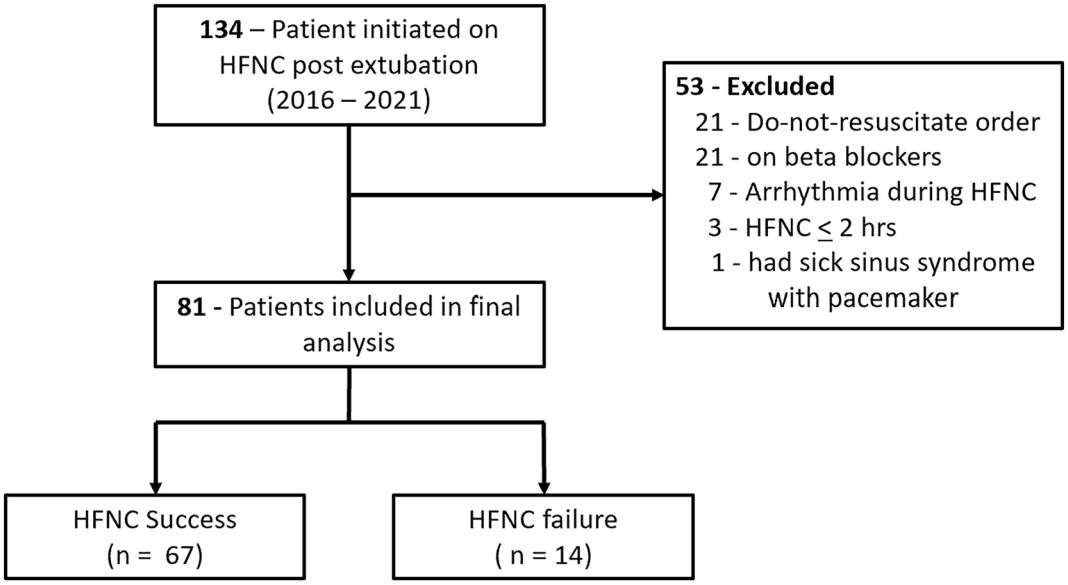

Fig. 1 STROBE figure

Index value of 3.0 (1.0–6.0), APACHE II score (at ICU admission) of 27 (IQR 23–30), and SOFA score of 7 (IQR 4–9) at ICU admission. Out of 81 patients, three-fourths ($n=61$, 75.3%) had at least 1 risk factor for extubation failure while nearly half of the patients ($n=38$, 46.9%) had 2 or more risk factors for extubation failure. At the time of HFNC initiation, the median FiO2 requirement was 40.0% (30.0%−45.0%) while the median flow rate of HFNC was 60L/min (IQR 55.0 −60.0). Seventy-five patients had both the pre- and post-ABGs available. Among these patients, the pre-ABG was performed at median 5.32 h before HFNC initiation (IQR 3.67–7.34), and post-ABG was performed at median 1.42 h after HFNC initiation (IQR 1.03–3.08).

14 patients (17.3%) had HFNC failure (6 were escalated to NIV, 8 were reintubated, none died within 48 h of HFNC usage, post-extubation). Of these, 11 patients failed due to worsening hypoxia, two due to depressed GCS with inability to protect their airways, (one with hypercapnia and other with worsening hemodynamic instability), and one due to sputum plugging. Majority of these (71.4%) HFNC failure patients had escalation of respiratory support within 24 h of HFNC initiation. Although the SOFA score (at ICU admission) in the HFNC failure group [8.5 (3.8–11.3)] was higher when compared to HFNC success [7.0 (4.0–9.0)], but the APACHE II (at ICU admission) and Charlson comorbidity index were similar in both these group. HFNC failure patients had poorer outcomes than the HFNC success group with higher ICU and hospital mortality (Table 1).

ROX, ROX-HR, ROX-HR-Flow at baseline vs 2, 6 and 12 h post-extubation

Table 2 shows the comparison of ROX, ROX-HR, ROX-HR Flow between HFNC success group and HFNC failure group. The time intervals considered were pre-HFNC initiation (baseline), 2, 6 and 12 h). In comparison to HFNC success group, the patients in the HFNC failure group had lower value of ROX, ROX-HR, ROX-HR-Flow at all these time intervals. The difference was statistically most significant at 2 h for all the 3 indices—ROX, ROX-HR and ROX-HR-Flow.

At 2, 6 and 12 h, there was an incremental increase in AUROC value in ROX-HR and ROX-HR-Flow when compared to ROX (Table 2). However, this incremental increase was not statistically significant (ROX-HR versus ROX; AUROC: 0.834 vs 0.822; p-value: 0.456 and ROX-HR-Flow versus ROX; AUROC: 0.854 vs 0.822; p-value: 0.348).

ROX versus POX-HR-Flow at pre- and post-HFNC interval

Table 3 shows the comparison of ROX and POX-HR-Flow between HFNC success group and HFNC failure group for the 75 patients who had pre- and post-HFNC ABGs available. ROX index and POX-HR-Flow were calculated at 2 time points, namely—pre-HFNC (last ABG prior to HFNC initiation) and post-HFNC (first ABG post-HFNC initiation). In comparison to HFNC success group, the patients in the HFNC failure group had statistically significant lower value of ROX index as well as POX-HR-Flow in the post-HFNC period. However, the AUROC were comparable.

Table 1 Baseline characteristics and outcomes of patients initiated on HFNC

	Total HFNC (n = 81)	HFNC success (n = 67)	HFNC Failure (n = 14)	p-value
Age	59.0 (45.5–69.0)	58.0 (46.0–69.0)	60.0 (39.5–69.5)	0.033*
Male gender	60 (74.1%)	52 (77.6%)	8 (57.1%)	0.181
BMI	25.1 (21.5–29.0)	25.1 (20.5–29.0)	25.3 (22.5–29.2)	0.591
APACHE II (at ICU admission)	27.0 (22.5–30.0)	26.0 (22.0–30.0)	28.0 (24.0–31.8)	0.326
SOFA Score (at ICU admission)	7.0 (4.0–9.0)	7.0 (4.0–9.0)	8.5 (3.8–11.3)	0.020*
Charlson Comorbidity Index	3.0 (1.0–6.0)	4.0 (1.0–6.0)	3.0 (1.0–8.3)	0.870
Diabetes mellitus	26 (32.1%)	22 (32.8%)	4 (28.6%)	0.760
Hypertension	33 (40.7%)	27 (40.3%)	6 (42.9%)	0.861
Ischaemic heart disease	19 (23.5%)	15 (22.4%)	4 (28.6%)	0.625
Chronic liver disease	5 (6.2%)	4 (6.0%)	1 (7.1%)	0.870
Chronic kidney disease	9 (11.1%)	8 (11.9%)	1 (7.1%)	0.609
Cerebrovascular accident	11 (13.6%)	9 (13.4%)	2 (14.3%)	0.934
Asthma/COPD	7 (8.6%)	6 (9.0%)	1 (7.1%)	0.829
Covid-19	6 (7.4%)	4 (6.0%)	2 (14.3%)	0.424
Pneumonia	62 (76.5%)	52 (77.6%)	10 (71.4%)	0.625
Other respiratory conditions	3 (3.7%)	3 (4.5%)	0 (0.0%)	0.942
Immunocompromised	7 (8.6%)	5 (7.5%)	2 (14.3%)	0.415
Cuff leak	69 (85.2%)	58 (86.6%)	11 (78.6%)	0.450
Moderate–large respiratory secretions	25 (30.9%)	23 (34.3%)	2 (14.3%)	0.090
Vasopressor support at time of HFNC initiation	6 (7.4%)	2 (3.0%)	4 (28.6%)	0.064
Surgical cases	29 (35.8%)	24 (35.8%)	5 (35.7%)	0.994
GCS Motor Score at time of extubation	6.0 (6.0–6.0)	6.0 (6.0–6.0)	6.0 (6.0–6.0)	0.48
Fluid balance 24 h prior to extubation	231.0 (−296.9–998.0)	217.8 (−383.7–997.0)	538.2 (−245.6–2839.1)	0.240
Duration of MV days	5.0 (3.0–8.0)	5.0 (3.0–9.0)	3.0 (2.0–6.5)	0.301
Patients with at least one risk factor for extubation failure	61 (75.3%)	49 (73.1%)	12 (85.7%)	0.322
Patients with > / = 2 risk factors for extubation failure	38 (46.9%)	32 (47.8%)	6 (42.9%)	0.741
Vital signs pre-HFNC initiation				
Heart rate	90.0 (80.5–97.0)	88.0 (80.0–100.0)	93.0 (88.3–97.0)	0.574
Respiratory rate	21.0 (18.0–25.0)	21.0 (18.0–25.0)	19.0 (17.0–21.5)	0.095
SpO2, %	97.0 (95.0–99.0)	97.0 (95.0–99.0)	98.0 (94.8–100.0)	0.353
Arterial blood gas analysis pre-HFNC initiation				
pH	7.44 (7.39–7.47)	7.45 (7.39–7.47)	7.42 (7.39–7.45)	0.105
PaO2	76.8 (68.6–84.7)	73.3 (67.3–82.0)	91.2 (79.4–103.6)	0.088
PF ratio	243.3 (199.1–294.4)	243.3 (196.9–291.0)	252.8 (229.2–333.2)	0.378
PaCO2, mmHg	36.7 (33.0–41.6)	36.5 (32.0–41.6)	37.5 (35.5–41.5)	0.272
Bicarbonate, mmol/L	23.0 (21.0–27.1)	23.0 (20.9–27.5)	23.0 (21.0–26.8)	0.866
HFNC initiation settings and outcomes				
Initial HFNC flow	60.0 (55.0–60.0)	60.0 (50.0–60.0)	60.0 (57.5–60.0)	0.691
Initial FiO2 set on HFNC	40.0 (30.0–45.0)	40.0 (30.0–40.0)	42.5 (40.0–50.0)	0.012*
Duration of HFNC in hours	20.5 (12.1–27.2)	21.4 (13.6–27.3)	15.0 (7.8–26.6)	0.179
ICU stay duration	7.0 (5.0–13.0)	7.0 (5.0–13.0)	9.5 (6.0–14.3)	0.284
ICU mortality	5 (6.2%)	1 (1.5%)	4 (28.6%)	0.046*
Hospital stay duration	28.0 (13.0–38.0)	30.0 (14.0–38.0)	17.0 (9.5–34.3)	0.103
Hospital mortality	9 (11.1%)	4 (6.0%)	5 (35.7%)	0.024

Values are expressed in number (percentage) and median (interquartile range)

*P-value < 0.05; **P-value < 0.01

APACHE Acute Physiology and Chronic Health Evaluation, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *GCS* Glasgow coma score, *HFNC* high-flow nasal cannula, *ICU* intensive care unit, *IQR* interquartile range, *MV* mechanical ventilation, *PF ratio* PaO2/FiO2, *SOFA* Sequential Organ Failure Assessment

Table 2 Variables and diagnostic accuracy for HFNC outcomes (n = 81)

	No. of patients who remain on HFNC	HFNC success	No. of patients who remain on HFNC	HFNC failure	P-value	AUROC
ROX						
Before initiation of HFNC	67	15.15 (11.90–17.71)	14	14.09 (11.15–16.75)	0.359	0.578 (0.422–0.734)
2 h	67	14.41 (10.67–20.00)	14	7.87 (6.52–11.40)	< 0.001**	0.822 (0.695–0.949)
6 h	60	13.05 (10.92–18.47)	11	8.75 (5.64–18.94)	0.015*	0.731 (0.525–0.937)
12 h	53	13.06 (10.45–17.01)	10	8.34 (6.35–15.67)	0.077	0.677 (0.450–0.904)
ROX-HR						
Before initiation of HFNC	67	17.22 (12.63–21.01)	14	15.63 (12.52–19.63)	0.284	0.591 (0.445–0.737)
2 h	67	16.04 (11.67–22.30)	14	8.44 (6.28–11.87)	< 0.001**	0.834 (0.719–0.949)
6 h	60	14.62 (11.08–20.56)	11	8.75 (5.64–18.94)	0.006**	0.763 (0.585–0.941)
12 h	53	14.94 (10.98–20.07)	10	9.87 (5.58–19.43)	0.094	0.668 (0.447–0.889)
ROX-HR-flow						
Before initiation of HFNC	67	17.80 (14.17–23.17)	14	17.27 (12.52–20.72)	0.355	0.579 (0.430–0.728)
2 h	67	18.38 (12.72–24.32)	14	8.77 (6.28–11.95)	< 0.001**	0.854 (0.756–0.952)
6 h	60	18.25 (11.66–27.01)	11	8.75 (5.64–18.94)	0.002**	0.794 (0.636–0.952)
12 h	53	17.40 (14.42–23.94)	10	9.87 (5.58–19.43)	0.020*	0.734 (0.539–0.929)

* *P*-value < 0.05; ** *P*-value < 0.01

Table 3 Variables and diagnostic accuracy for HFNC outcomes at the time of ABG taken (n = 75)

		No. of patients who remain on HFNC	HFNC success	No. of patients who remain on HFNC	HFNC failure	P-value	AUROC
ROX	Pre-HFNC#	62	15.09 (11.55–17.45)	13	14.29 (10.80–17.02)	0.566	0.551 (0.387–0.715)
	Post-HFNC##	62	12.79 (9.95–19.22)	13	9.10 (7.09–11.01)	0.003**	0.767 (0.623–0.911)
POX-HR-flow	Pre-HFNC#	62	13.39 (10.15–21.64)	13	12.05 (9.38–20.58)	0.769	0.526 (0.359–0.693)
	Post-HFNC##	62	15.27 (8.53–20.91)	13	8.09 (5.62–10.86)	0.003**	0.767 (0.629–0.904)

*P-value < 0.05; **P-value < 0.01, # 5.32 h (IQR 3.67–7.34) pre-HFNC initiation, ## 1.42 h (IQR 1.03–3.08) post-HFNC initiation

Cut-offs of ROX, ROX-HR, ROX-HR flow and POX-HR flow

Based on ROC curves at 2 h for ROX, ROX-HR, and ROX-HR-Flow and post-HFNC initiation for POX-HR-Flow (1.42 h, IQR 1.03–3.08) and using AUROC of more than 0.7 for prediction of HFNC success, a cut-off value of 12.4, 12.13, 12.25 and 10.45 were determined for ROX, ROX-HR, ROX-HR-Flow and POX-HR-Flow, respectively (Table 4). At 2 h, ROX-HR-Flow index had the best sensitivity and specificity with highest Youden score.

Kaplan–Meier plots were generated to visualize HFNC success probability based on the cut-off values determined for ROX, ROX-HR, ROX-HR-Flow at 2 h post-HFNC initiation, and POX-HR-Flow post-HFNC initiation (Fig. 2A–D). For all four indices, patients with values above the determined cut-offs consistently demonstrated a higher probability of HFNC success over the 48-h follow-up period compared to those below the cut-offs. The separation between the curves for patients

Table 4 Prediction of HFNC success based on cut-offs

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	LR +	LR-	Youden index
2 h ROX > 12.40	65.7	85.7	34.3	95.7	4.59	0.40	0.514
2 h ROX-HR > 12.13	71.6	85.7	38.7	96.0	5.01	0.33	0.573
2 h ROX-HR Flow > 12.25	77.6	85.7	44.4	96.3	5.43	0.26	0.633
Post-HFNC POX-HR flow > 10.45[#]	74.2	76.9	38.5	93.9	3.21	0.34	0.511

1.42 h (IQR 1.03–3.08) post-HFNC initiation

NPV negative predictive value, *PPV* positive predictive value, *LR* likelihood ratio

above and below the cut-offs was statistically significant for all indices, as indicated by the log-rank test. Notably, the ROX-HR-Flow index at 2 h post-HFNC initiation (Fig. 2C) showed the most pronounced separation between the curves, with patients above the cut-off of 12.25 maintaining a markedly higher probability of HFNC success. This visual trend aligns with the finding that ROX-HR-Flow at 2 h had the best prediction accuracy with the highest AUROC of 0.854. These observations further support the potential of the modified indices, particularly ROX-HR-Flow at 2 h, for early and accurate prediction of HFNC outcomes in the post-extubation setting (Fig. 3).

Multivariate regression analysis

On univariate and multivariate COX proportional regression analysis, ROX as well as all the three modified variables were significantly associated with a lower risk of HFNC failure (Table 5). The variables included in the multivariate analysis were age, gender, respiratory rate at time of HFNC initiation, number of patients with moderate–large respiratory secretions and SOFA score at ICU admission.

Other variables included in the multivariate analysis were age, gender, respiratory rate at time of HFNC initiation, number of patients with moderate–large respiratory secretions, and SOFA score.

Post hoc power calculation based on our observed HFNC failure rate suggested that a sample size of 160 would be required to have an adequately powered study. However, we only had 81 patients who met the inclusion criteria over the 6-year study period. AUROC with internal variances was calculated; the lower border of the interval was higher than 0.5.

Discussion

Our retrospective study suggests that the modified ROX indices can better predict HFNC outcomes in the post-extubation setting, as early as 2 h post-HFNC initiation. ROX-HR-Flow 2 h post-HFNC initiation appears most promising. To the best of our knowledge, our study is the first to investigate the incorporation of flow rate as well substitution with PF ratio in the ROX index in this setting. Additionally, our study further confirms the importance of incorporating HR in concordance with the previous study of post-extubation HFNC usage [13].

Early recognition of the need for reintubation, which has inverse association with poor outcomes including mortality, is an important clinical decision [11]. Indices like ROX-HR-Flow with slightly better prediction compared to ROX index, may be very useful for early assessment during the post-extubation period. ROX index was initially developed and validated among the patients with ARF to provide outcome prediction at 12 h. Subsequent studies among ARF as well post-extubation patients highlighted early outcome prediction as early as 2 h [9, 13]. Additionally, previous studies suggested that modified ROX indices may predict outcomes early in both of these settings [9, 13, 23]. Our study expands the existing knowledge regarding early prediction of HFNC failure in the post-extubation setting.

There are very few studies that have investigated the role of ROX index in the post-extubation setting [9, 13, 20]. ROX index appears valid in this setting; although, with different cut-offs. In our study, the cut-off value for ROX at 2 h was 12.4 as compared to 7–8.7 in previous studies at 2–12 h post-HFNC initiation [9, 13, 20]. The variation in cut-off values for ROX has been well described in the ARF setting as well [34]. This difference could be due to heterogenicity of study population as well as aetiology of respiratory failure. Our study population included 35% surgical patients, compared to only medical ICU patients in the other studies [9, 13, 20]. Study by Goh et al. study had a much higher proportion of pneumonia patients with immunocompromised status compared to our study [13]. Thus, the results of our study may be more generalizable and replicable across wider spectrum of critically ill patients.

With regard to newer modified variables, ROX-HR has previously been studied to predict HFNC outcome in the post-extubation HFNC setting in a prospective, smaller 46-patient study, demonstrating better outcome prediction compared to ROX index [13]. Although retrospective, our study is the largest study till date to evaluate this aspect and adds to this body of evidence suggesting incorporation of HR. Additionally, as compared to the

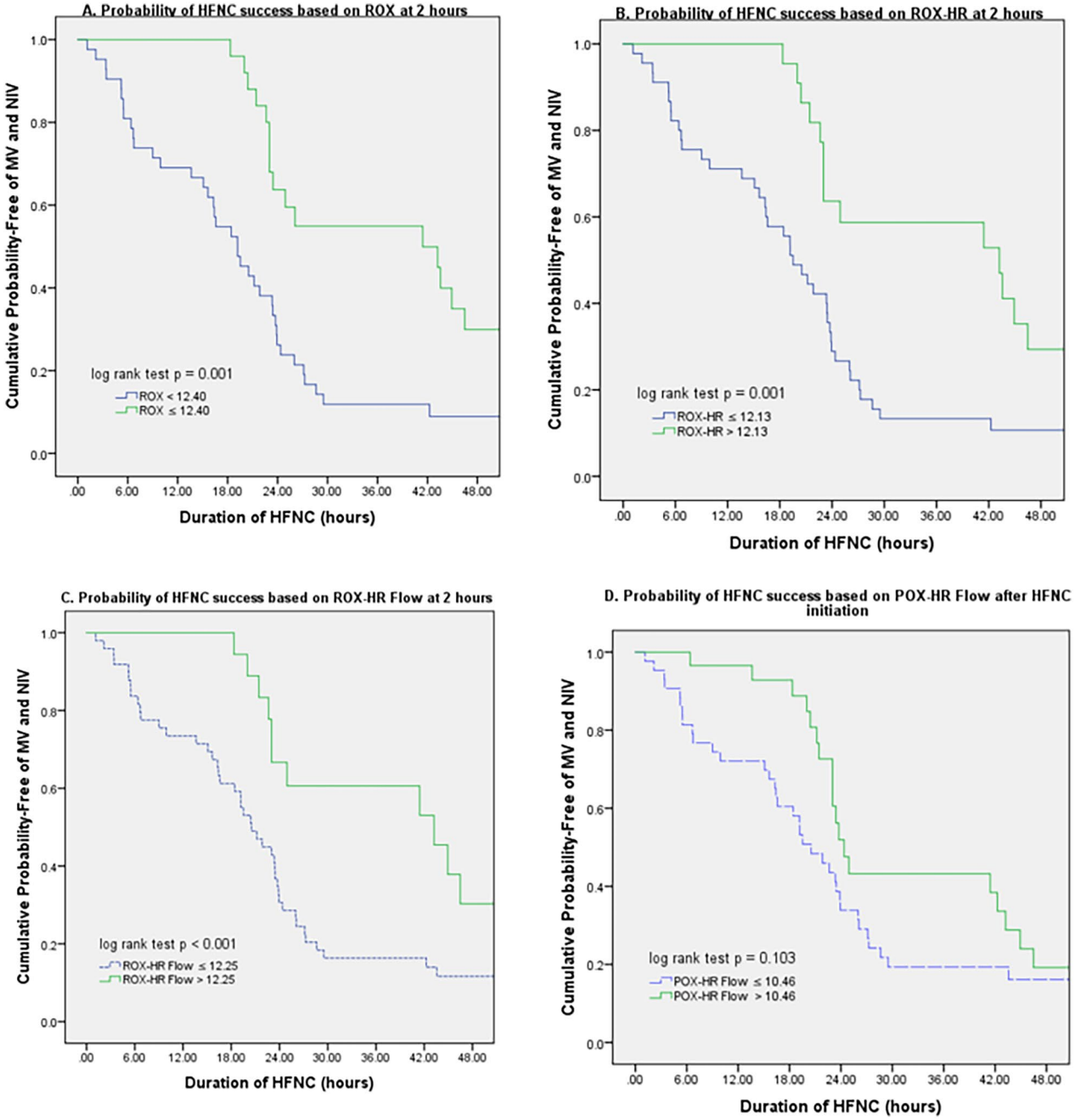

Fig. 2 **A**–**D** Kaplan–Meier plots of HFNC success probability based on ROX, ROX-HR, ROX-HR Flow index at 2 h and POX-HR Flow index after HFNC initiation for post-extubation patients

previous study, we excluded patients who were on beta-blocker therapy, had a pacemaker and those with arrhythmia; to avoid the interference with heart rate response.

Flow rate of HFNC has been shown to be associated with better oxygenation as well as reduction in respiratory rate, and therefore likely to influence the ROX index [27]. To the best of knowledge, no study has been done so far to study whether modification of ROX index with incorporation of HFNC flow rate would improve its predictability. Similarly, PF ratio has not been studied in post-extubation settings, despite emerging evidence in the ARF settings [22, 23]. In our study, POX-HR-Flow was comparable to ROX in predicting post-extubation HFNC outcomes.

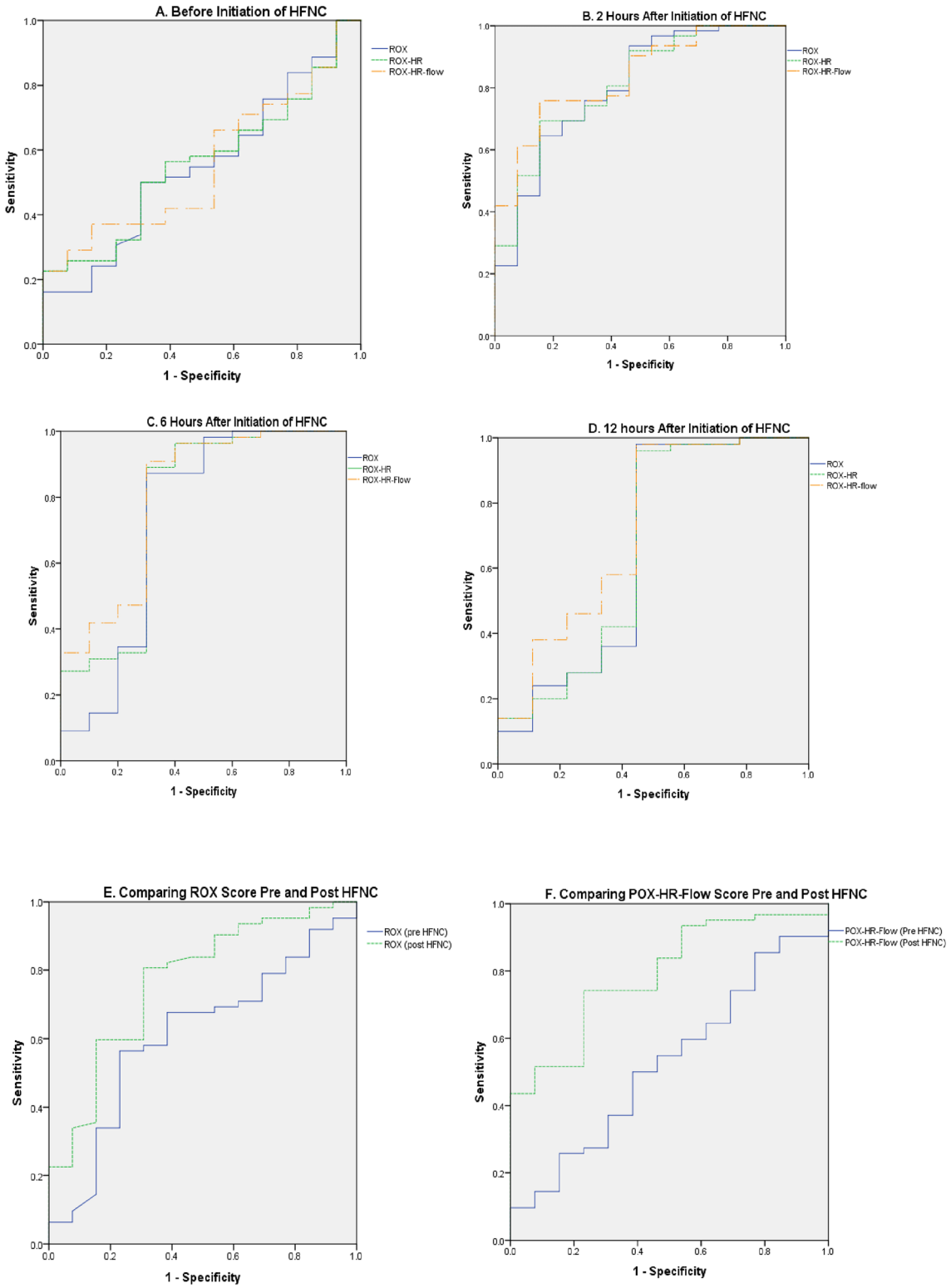

Fig. 3 The AUROC curves for the comparison between ROX, ROX-HR, and ROX-HR-Flow scores are displayed at various time points: A prior to the initiation of HFNC, B 2 h post-initiation, C 6 h post-initiation, and D 12 h post-initiation. Additionally, AUROC comparisons between pre- and post-HFNC periods are shown for E ROX score and F POX-HR-Flow score

Table 5 Cox regression analysis evaluating for the prediction of HFNC failure in patients post-extubation

	Univariate analysis	p-value	Multivariate analysis	p-value
2 h ROX > 12.40	0.183 (0.041–0.828)	0.027*	0.125 (0.026–0.601)	0.009**
2 h ROX-HR > 12.13	0.142 (0.032–0.641)	0.011*	0.057 (0.010–0.318)	0.001**
2 h ROX-HR Flow > 12.25	0.106 (0.024–0.474)	0.003**	0.029 (0.005–0.185)	< 0.001**
POX-HR Flow > 10.45	0.156 (0.043–0.568)	0.005**	0.064 (0.013–0.305)	0.001**

* P-value < 0.05; **P-value < 0.01

Our study population was similar to previous studies of HFNC failure in many ways. The post-extubation HFNC failure rate in our study was 17.3% which is comparable to what has been described in medical literature, 9.5–18.1% [7–9]. Three-fourths of the cases had pneumonia as the primary diagnosis which was similar in distribution among both HFNC success and HFNC failure group. Three–fourths of our study population (75.3%) had at least 1 risk factors for extubation failure while nearly half of them (46.9%) had 2 or more risk factors for extubation failure. This was comparable to a previous study done in Singapore population which also showed 78.7% of patients having at least 1 risk factor for extubation [7]. Similarly, another study done by Hernandez et al. had found that nearly half (53.9%) of the extubated patients were at high risk for reintubation [35].

Another strength of our study was that we used electronic medical records (EPIC®) to collect the data retrospectively. Therefore, we did not have any missing data, and that adds to the robustness of our results. However, several limitations exist. Firstly, ours was a small single-centre retrospective study, with risk of selection bias in view of retrospective design. The selection bias was addressed by enrolling all consecutive patients who were started on HFNC post-extubation during the study period. With regard to the sample size, our study is the largest published work to best of our knowledge that addresses these modified variables in the post-extubation setting. Post hoc power calculation based on our observed HFNC failure rate suggested that a sample size of 160 would be required to have an adequately powered study as against our sample size of 81. To mitigate this limitation, AUROC with internal variances was calculated. The lower border of the interval was higher than 0.5. Based on statistical interpretation, the model is not a random model, since the lower 95% confidence interval bound for the AUROC for 2 h ROX, ROX-HR, ROX-HR-Flow and post-HFNC POX-HR-Flow exceeds the 0.5, which is the minimum threshold in correctly classifying the data using the model [36].

Additionally, despite the smaller sample size, these positive results rule out Type 2 error. However, larger prospective studies are needed to test the hypothesis in future.

Additionally, there is a risk of overfitting in the studies with small sample size. We mitigated this risk by doing univariate analysis and selected variables that were both clinically and statistically significant for the multivariate analysis. The small sample size in our study poses challenges in generating reliable ROC/AUC estimates, as variability in small datasets may lead to over- or underestimation of predictive accuracy. The findings should be interpreted cautiously, and validation in larger datasets is needed to confirm their robustness. Recent advancements in predictive modelling, including ensemble methods and regularization techniques, offer potential solutions to address the challenges of small datasets, such as overfitting and instability in regression coefficients [37–39]. Additionally, machine learning approaches, as described in recent literature, provide opportunities to refine predictive models, but require rigorous validation to ensure clinical applicability [40, 41]. Future studies should explore these methodologies to enhance the robustness and generalizability of predictive models for HFNC outcomes. Moreover, selection of patients for post-extubation HFNC and the determination of failed HFNC was not protocolized in the institution ICU and was based on clinical judgment of the ICU team. To address this issue of lack of standardization, we used escalation to intubation or NIV as an objective parameter. We believe that any intubation/NIV criteria would have been applied equally to HFNC failure as well as success groups, in view of the consultant-led and round-the-clock respiratory therapist cover. Nonetheless, our intubation rate was comparable to previous studies. Similarly, recent reviews of HFNC usage have identified similar limitations of lack of data and significant heterogeneity among the published studies to be able to guide clinical practice in this setting [42]. Finally, we had excluded patients who were on beta-blockers and who had arrhythmia as that would affect the heart rate and hence, results of this study cannot be generalized to patients who are on beta-blockers and who have arrhythmias.

Conclusion

Our single-centre study suggests that in the setting of post-extubation HFNC usage, modified ROX indices can better predict HFNC outcomes, as early as 2 h post-HFNC initiation. ROX-HR-Flow appears most promising, using the proposed cut-offs of > 12.25 at 2 h to predict patients at low risk of HFNC failure. The findings of our retrospective study should be validated in larger prospective studies.

Author contributions

SG, WJDO and AK contributed to the literature search, conceptualization, study design, interpretation of data and writing of the draft manuscript. WJDO contributed to data analysis. SG, BZHC and WJDO contributed to data collection. SM, MGK and FAK contributed to reviewing and editing the manuscript. All the authors reviewed and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study has been approved by the National Healthcare Group (NHG) Domain-Specific Review Board (DSRB) with a waiver of informed consent due to the non-interventional retrospective study design (NHG DSRB reference number—2020/01167).

Consent for publication

All the authors have given their consent for publication of this article in this journal.

Competing interests

The authors declare no competing interests.

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