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A study on the prediction of the progression of respiratory failure using noninvasive indices in pediatric patients supported with high flow nasal cannula

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A study on the prediction of the progression of respiratory failure using noninvasive indices in pediatric patients supported with high flow nasal cannula

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Abstract

Background: High-flow nasal cannula (HFNC) is a useful respiratory support for children with respiratory distress; however, it elevates the risk of belated intubation. Recently, indices based on percutaneous oxygen saturation (SpO_2),a fraction of inspired oxygen (FiO_2), and respiratory rate (RR) have been suggested for predicting HFNC failure. We aimed to evaluate various indices predicting HFNC failure in children who started receiving HFNC at this tertiary center for 27months.

Methods: Cases of HFNC failure were classified as hypoxic respiratory failure (HRF) or non-HRF (NHRF) according to the cause of intubation. Ratio of SpO2 by FiO_2 (S/F), ratio of S/F by RR (ROX), ratio of S/F by RR/median RR (ROX-M), and ratio of S/F by z-score of RR (ROX-Z) were calculated and compared between groups.

Results: Of the 152 cases, 45 (29.6%) failed to wean off the HFNC support, of which 21 (46.7%) were HRFs and 24 (53.3%) were NHRFs. S/F and ROX-M at 6 and 3 hours, respectively, showed good predictability for predicting HRF with high area under the curve. Whereas initial hypercapnia and low weight were good predictors for NHRF.

Conclusions: For the management of children with HFNC, these risk factors and indicators should be monitored to make an

early decision of intubation.

Keyword: High-flow nasal cannula, Pediatric respiratory failure, Risk factors, ROX index, S/F ratio
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Chapter 1. Introduction

The high-flow nasal cannula (HFNC) is a device that produces heated and humidified air blended with oxygen at a high flow rate. The device generates positive pressure to the upper airways, prevents alveolar closure, and delivers a constant fraction of inspired oxygen (FiO_2) (1, 2). The use of this device has been reported to improve thoracic-abdominal coordination and increase end-expiratory lung impedance, thereby reducing the work of breathing in patients with dyspnea (3, 4). In addition, this technique has been reported to reduce intubation rates and mortality in patients with hypoxic respiratory failure (HRF) (5). As well as providing supplying high oxygen concentration and pressure, HFNC may help for patients with respiratory distress other than hypoxic cause, as it can reduce the preload in patients with heart failure or wash out carbon dioxide in the airways in patients with hypercapnia (1, 6).

However, there are concerns about delays in escalating the respiratory support such as mechanical ventilation using endotracheal tube or non-invasive method, and it is known to be associated with adverse consequences such as intensive care unit mortality and extubation failure in adult studies (7). There have been several studies on the early detection of HFNC failure, and the ROX index was first presented by Roca et al. (8). The index was calculated as the ratio of percutaneous oxygen saturation (SpO_2) to FiO_2 divided by respiratory rate (RR), and lower values predicted the eventual need for intubation. Similar studies have been reported in adult patients with hypoxic respiratory distress treated with HFNC for pneumonia or COVID-19 infection (9-11). Using the z-score of RR instead of RR, the pediatric ROX index calculated 24 hours after HFNC initiation showed predictability of HFNC failure in children with tachypnea (12).

Although these studies evaluated only patients with hypoxic respiratory distress, respiratory acidosis or airway problems are also major problems in deciding whether to maintain HFNC or intubation (1). Therefore, the study hypothesized that indicators such as S/F ratio, ROX and modified ROX indices could predict HFNC failure in a heterogeneous patient population, considering that there are various conditions that consider HFNC supply. We also sought to analyze the risk factors for HFNC failure.

Chapter 2. Methods

1.1. Study design and patients

This study is a retrospective review of the medical records of patients aged <18 years who were admitted to Seoul National University Hospital for respiratory failure and treated with HFNC. We included all patients who started HFNC treatment in general wards, pediatric intensive care units, and pediatric emergency centers from June 2019 to August 2021 and did not receive mechanical ventilation 24 hours before the initiation of HFNC. We excluded patients who had previously decided not to intubate or had undergone elective intubation for surgery or examination, such as bronchoscopy. Patients with a SpO_2 target below 92% due to cyanotic heart disease or who were discharged or transferred while maintaining HFNC support were also excluded.

1.2. Clinical data

Patient sex, age, weight, height, underlying disease, and clinical diagnosis were collected at the start of HFNC application. The underlying disease was assessed by examining whether the patient had any known neuromuscular, respiratory, cardiovascular, malignant, immunocompromised, or other diseases not classified at the time of respiratory failure. To evaluate the patient's chronic respiratory status, oxygen demand, and venous partial pressure of carbon dioxide ($PvCO_2$) in a stable state obtained at an outpatient clinic or previous hospitalization were reviewed. Vital signs such as blood pressure, heart rate, RR, body temperature, and SpO_2, the status of respiratory acidosis such as venous pH and $pvCO_2$, and indicators of other organ failures such as lactate, platelet, bilirubin, and creatinine just before the initiation of HFNC were also collected. HFNC settings such as FiO_2 and flow rate and patient-derived

factors, such as RR and SpO_2, during HFNC application were recorded to calculate the indices.

The nutritional status of the patients was assessed as z-scores of weight for age and weight for height. The z-scores were calculated based on the World Health Organization growth curve for children up to 35 months of age (13) and based on the Korean growth chart for children and adolescents aged 3 years and older (14). Underweight was defined as weight for age less than -2 standard deviation (SD) (15).

1.3. HFNC therapy and treatment failure

Patients who were able to wean HFNC support during hospitalization were classified into the success group, and those who eventually required noninvasive ventilation (NIV) or intubation for mechanical ventilation were classified into the failure group. Patients in the failure group were sub-divided into HRF and non-HRF (NHRF) groups according to the reason for the decision to apply the ventilator. The decision was made by the clinician according to the following indications: 1) unstable vital signs or altered mental status; 2) hypoxemia with SpO_2 below 92% despite the support of HFNC with high FiO_2; 3) patients whose airways were not patent for reasons such as decreased muscle tone or secretions; and 4) severe respiratory acidosis that did not improve (1, 5, 16, 17). Among them, patients who showed unstable oxygenation with SpO_2 of less than 92% at $FiO_2 \geq 0.5$, just before applying ventilator, were classified into the HRF, and the other failure cases were classified as NHRF.

HFNC equipment (AIRVO2, Fisher & Paykel Healthcare, Auckland, New Zealand) was used. The flow rate was adjusted to 1–2 L/min/kg from a minimum of 2 L/min to a maximum of 60 L/min according to the improvement or worsening of patients' symptoms

and signs or tolerability. FiO_2 was set to maintain SpO_2 above 92%. The initial setting was a flow rate of 1L/min/kg and FiO2 of 0.3. The flow rate was adjusted according to the degree of improvement in respiratory symptoms such as chest retraction and tachypnea, or the status of hypercapnia. For patients showing SpO2<92% with low flow oxygen supply, the initial flow rate was set to 1L/min/kg and FiO2 to 0.6. If the oxygen supply was not adequate in this setting, the flow rate was increased, and if the oxygen supply was tolerable, the FiO2 was decreased. The setting was decided by the clinician according to each patient requirement. The flow temperature was set at 34℃ and, at the subject's request, changed to 31℃.

1.4. S/F, ROX, and its age-modified forms

We calculated the S/F as SpO_2 (%) divided by FiO_2. ROX was calculated as S/F divided by RR, and modified ROX was calculated by substituting the RR in ROX with the RR adjusted for age. In the case of ROX-M, a ratio of RR to median RR of the same age was used, and in the case of ROX-Z, a z-score of RR according to age was used for substitution. The calculation formula is as follows: The median RR and z-score of RR were calculated based on RR distribution in Korean children (18).

$$S/F = \frac{SpO2\ (\%)}{FiO2}$$

$$ROX = \frac{S/F}{RR(/min)}$$

$$ROX - M = \frac{S/F}{RR(/min)/median\ RR(/min)}$$

$$ROX - Z = \frac{S/F}{Z - score\ of\ RR}$$

Initial indices measured at the time of applying HFNC (0h) and timely indices at 1, 3, 6, 12, 18 and 24 hours after the initiation of HFNC were compared in each group. In addition, the worst values of the indices within the first 24 hours after HFNC application were collected and labeled as WoSF, WoROX, WoROX-M, and WoROX-Z, respectively.

1.5. Statistical analysis

Binary and categorical values are summarized as counts and percentages. Continuous variables are expressed as mean ± SD for normally distributed data according to the Shapiro-Wilk test and as median (interquartile range) otherwise. The chi-square test or Fisher's exact test was used to compare the categorical values. For continuous values, Student's t-test or Mann-Whitney U test was used to compare two groups, and the ANOVA test or Kruskal-Wallis test was used to compare three groups with post-hoc analysis using the Bonferroni method. The censored value was applied to ROX-Z when the z-score of the RR was no greater than 0. Thus, ROX-Z was considered non-normally distributed.

Receiver operating characteristic (ROC) curve analysis was performed to assess the best cutoff of each index for predicting HFNC outcomes. Outcomes were assessed in two ways to determine whether the indicators reflect a specific type of dyspnea: overall HFNC failure, including HRF and NHRF, and HRF alone. The area under the ROC curve (AUC) of each index was calculated and compared using Delong's test. The best cutoff values were calculated using Youden's index. We also performed univariate and multivariate logistic regression analyses of the risk factors for HFNC failure. Statistical analyses were performed using the R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-

sided p value of <0.05. This study was approved by the Institutional Review Board of the Seoul National University Hospital (approval number: H-2108-209-1249). The requirement for written consent was waived due to the retrospective nature of the study and the minimal risk.

Chapter 3. Results

There were 230 cases of HFNC initiation, and a total of 78 patients were excluded: 17 patients had decided not to intubate before respiratory symptoms occurred, 38 patients underwent elective intubation, 11 patients had cyanotic heart disease, 11 patients were discharged or transferred to another hospital while maintaining HFNC, and the other one case had no recorded RR during the first 24 hours. Of the 152 patients, HFNC was successfully removed in 107 (70.4%) patients, who were classified into the success group. Thirty-three patients were intubated and 12 were treated with NIV; these patients were classified into the failure group. Of these 45 patients, 21 were classified as HRFs and the other 24 were classified as NHRFs. Among the NHRF patients, 20 showed severe acidosis and the other four were suspected of having airway problems because of frequent and intermittent desaturation or severe retraction that did not improve with HFNC (Figure 1).

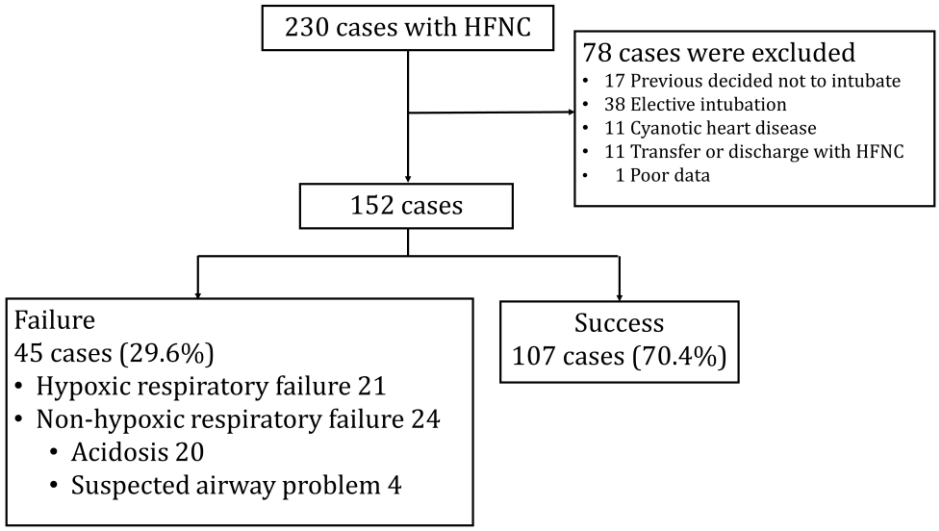

Figure 1. Flowchart showing study enrollment of patients with a high-flow nasal cannula (HFNC) and classification according to respiratory failure.

Of all participants, 89 (58.6%) were male and median age was 2.3 (0.6–7.4) years. Most patients had comorbidities (90.8%), of which neuromuscular disease was the most common, followed by respiratory, cardiovascular, and malignant diseases. There were no differences between the two groups in baseline $PvCO_2$, the proportion of underlying disease, and distribution of clinical diagnosis. The major diagnoses of respiratory failure were pneumonia or bronchiolitis (47.4%), heart failure (18.4%), atelectasis (11.8%), and airway diseases (8.6%). The median duration of HFNC was 3.4 (1.5–6.1) days in the success group and 1.3 (0.8–3.1) days in the failure group, which was longer in the success group (P=0.001) (Table 1).

Table 1. Characteristics of patients

	All patients (N=152)	Success (N=107)	Failure (N=45)	P
Sex (F/M)	63/89	38/69	25/20	0.035
Age (yr)	2.3 (0.6–7.4)	2.4 (0.7–7.1)	2.2 (0.5–7.8)	0.548
Z-score of weight for age	−1.5 ± 2.2	−1.2 ± 2.1	−2.1 ± 2.3	0.030
Z-score of weight for height	0.1 ± 2.4	0.2 ± 2.1	−0.2 ± 2.9	0.366
Underweight	89 (58.6%)	40 (37.7%)	26 (57.8%)	0.036
Chronic O_2 need	32 (21.1%)	25 (23.4%)	7 (15.6%)	0.390
baseline $PvCO_2$	43.1 (39.9–49.9)	44.0 (40.8–50.3)	42.0 (38.0–48.0)	0.270
Underlying disease	138 (90.8%)	96 (89.7%)	42 (93.3%)	0.759
Neuromuscular disease	41 (27.0%)	26 (24.3%)	15 (33.3%)	0.344
Respiratory disease	31 (20.4%)	20 (18.7%)	11 (24.4%)	0.560
Cardiovascular disease	26 (17.1%)	18 (16.8%)	8 (17.8%)	1
Malignancy	24 (15.8%)	17 (15.9%)	7 (15.6%)	1
Immunocompromised	10 (6.6%)	6 (5.6%)	4 (8.9%)	0.483
Others	11 (7.2%)	8 (7.5%)	3 (6.7%)	1
Diagnosis				0.202
Pneumonia/bronchiolitis	72 (47.4%)	50 (46.7%)	22 (48.9%)	
Heart failure	28 (18.4%)	20 (18.7%)	8 (17.8%)	
Atelectasis	18 (11.8%)	13 (12.1%)	5 (11.1%)	
Croup/Airway	13 (8.6%)	6 (5.6%)	7 (15.6%)	
Others	21 (13.8%)	18 (16.8%)	3 (6.7%)	
Duration	2.8 (1.0–5.4)	3.4 (1.5–6.1)	1.3 (0.8–3.1)	0.001

yr=years, $PvCO_2$=venous partial pressure of carbon dioxide

When we compared the worst respiratory indices within the first 24 hours between the success and failure groups, all four indices except WoROX-Z in the failure groups were significantly smaller than the ones in the success group (WoSF, 202.1 (152.0-242.5) vs 240.0 (199.0-318.3), P<0.001; WoROX, 4.1 (3.2-5.4) vs 5.5 (3.8-7.9), P=0.003; WoROX-M, 116.7 (82.4-162.3) vs 155.4 (94.5-216.3), P=0.008; WoROX-Z, 40.6 (23.6-76.0) vs 63.9 (30.1-118.3), P=0.050). ROC curve analysis of the four worst indices within the first 24 hours showed that these indices were insufficient to predict the failure of HFNC (AUC for WoSF 0.693, WoROX 0.652, WoROX-M 0.636, and WoROX-Z 0.669) (Table 2).

Table 2. Diagnostic value of worst parameter during 24 hours after initiation of high flow nasal cannula

	Success (N=107)	Failure (N=45)	P	AUC	Sensitivity	Specificity	cutoff value
WoSF	240.0 (199.0-318.3)	202.1 (152.0-242.5)	<0.001	0.693 (0.604-0.782)	0.62	0.71	217.478
WoROX	5.5 (3.8-7.9)	4.1 (3.2-5.4)	0.003	0.652 (0.559-0.745)	0.67	0.64	4.681
WoROX-M	155.4 (94.5-216.3)	116.7 (82.4-162.3)	0.008	0.636 (0.542-0.729)	0.53	0.7	123.225
WoROX-Z	63.9 (30.1-118.3)	40.6 (23.6-76.0)	0.050	0.601 (0.503-0.669)	0.78	0.45	76.785

AUC=area under the ROC curve

Table 3 summarizes the patient characteristics of the success, HRF, and NHRF groups. There was no difference in sex, age, and the proportion of underlying disorders and diagnoses, baseline O_2 need and $PvCO_2$. The z-score of weight for age was significantly different between the three groups (P=0.004) with the value in the NHRF group being significantly smaller than that of the success group in the post-hoc analysis (P=0.0039). The ratio of underweight patients was different between groups (P=0.020); the proportion of underweight was higher in the NHRF group than the success group in the post-hoc analysis (P=0.010). The $PvCO_2$ checked immediately before HFNC application did not differ between the groups (P=0.077); however, the proportion of patients with a $PvCO_2$ above 65 mmHg was higher in the NHRF group than in the success group (50.0% vs 21.0%, P=0.008 in the post-hoc analysis). Other parameters about initial characteristics such as initial vital signs, laboratory findings and settings of HFNC were summarized at Table 4.

Table 3. Clinical data according to 3 groups

	Success (n=107)	HRF (n=21)	NHRF (n=24)	P
Sex (F/M)	38/69	11/10	10/14	0.067
Age (yr)	2.4 (0.7–7.1)	3.7 (1.0–10.2)	1.0 (0.4–5.8)	0.211
Z-score of weight for age†	−1.2 ± 2.1	−1.2 ± 1.7	−2.8 ± 2.4	0.004
Z-score of weight for height	0.2 ± 2.1	0.5 ± 2.9	−0.9 ± 2.9	0.095
Underweight†	38 (35.5%)	9 (42.9%)	16 (66.7%)	0.020
Chronic O_2 need	25 (23.4%)	3 (14.3%)	4 (16.7%)	0.671
Baseline $PvCO_2$	44.0 (40.8–50.3)	41.6 (37.7–46.0)	43.3 (38.5–48.9)	0.399
Underlying disease	96 (89.7%)	19 (90.5%)	23 (95.8%)	0.824
Neuromuscular disease	26 (24.3%)	7 (33.3%)	8 (33.3%)	0.519
Respiratory disease	20 (18.7%)	2 (9.5%)	9 (37.5%)	0.061
Cardiovascular disease	18 (16.8%)	3 (14.3%)	5 (20.8%)	0.842
Malignancy	17 (15.9%)	4 (19.0%)	3 (12.5%)	0.883
Immunocompromised	6 (5.6%)	2 (9.5%)	2 (8.3%)	0.667
Others	8 (7.5%)	0 (0.0%)	3 (12.5%)	0.217
Diagnosis				0.209
Pneumonia/bronchiolitis	50 (46.7%)	13 (61.9%)	9 (37.5%)	
Croup/Airway	6 (5.6%)	1 (4.8%)	6 (25.0%)	
Heart failure	20 (18.7%)	4 (19.0%)	4 (16.7%)	
Atelectasis	13 (12.1%)	2 (9.5%)	3 (12.5%)	
Others	18 (16.8%)	1 (4.8%)	2 (8.3%)	
$PvCO_2$ (mmHg)	51.6 (41.9–61.8)	52.4 (42.2–61.4)	63.0 (48.5–75.7)	0.077
$PvCO_2$ > 65mmHg†	21 (21.0%)	5 (23.8%)	12 (50.0%)	0.020
Duration (day)‡	3.4 (1.5–6.1)	1.4 (1.0–3.1)	1.2 (0.6–4.4)	0.004

HRF=hypoxic respiratory failure; NHRF=non-hypoxic respiratory failure; yr =years; $PvCO_2$=venous partial pressure of carbon dioxide

†The values were significantly different between the NHRF group and the success group, and there was no difference between the other groups in post-hoc analysis.

‡Duration of high-flow nasal cannula was lower in the NHRF group than in the success group, and there was no difference between the other groups in post-hoc analysis.

Table 4. Clinical data and setting of high flow nasal cannula at initiation of respiratory support

	Success (n=107)	HRF (n=21)	NHRF (n=24)	P
sBP (mmHg)	103.0 (94.0–114.0)	103.0 (92.0–111.0)	103.0 (92.5–118.0)	0.975
dBP (mmHg)	62.6 ± 14.9	62.5 ± 15.9	68.4 ± 14.0	0.128
HR (/min)	134.6 ± 27.3	137.4 ± 26.4	145.0 ± 29.0	0.102
HR/median HR	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	0.367
Z-score of HR	1.2 ± 1.4	1.6 ± 1.2	1.4 ± 1.3	0.317
RR (/min)	40.0 (32.0–52.0)	40.0 (36.0–48.0)	43.0 (32.0–52.0)	0.955
RR/median RR	1.5 (1.2–1.9)	1.6 (1.3–1.9)	1.4 (1.0–1.7)	0.287
Z-score of RR	2.5 (1.1–5.1)	3.6 (2.2–7.2)	2.0 (0.3–4.2)	0.155
BT (℃)	37.1 (36.8–37.7)	37.4 (37.0–37.9)	37.0 (36.7–38.1)	0.279
SpO_2 (%)	98.0 (95.0–100.0)	96.0 (93.0–98.0)	98.0 (96.0–100.0)	0.109
Venous pH	7.3 (7.3–7.4)	7.3 (7.3–7.4)	7.3 (7.2–7.3)	0.056
$PvCO_2$ (mmHg)	51.6 (41.9–61.8)	52.4 (42.2–61.4)	63.0 (48.5–75.7)	0.077
Lactate (mmol/L)	1.4 (0.9–2.3)	1.8 (1.4–2.5)	1.5 (1.2–1.9)	0.722
Platelet ($X10^3/\mu L$)	250.0 (142.0–344.0)	175.0 (110.0–417.0)	258.0 (194.0–390.5)	0.564
Bilirubin (mg/dL)	0.5 (0.3–0.7)	0.5 (0.4–0.7)	0.4 (0.3–0.8)	0.809
Creatinine (mg/dL)	0.4 (0.4–0.5)	0.4 (0.4–0.5)	0.4 (0.4–0.5)	0.751
Flow (L/min)	15.0 (10.0–23.5)	18.0 (12.0–25.0)	8.0 (6.0–15.0)	0.002
Flow/weight (L/min/kg)	1.2 (0.9–1.6)	1.1 (0.7–2.0)	1.2 (0.7–1.7)	0.815
FiO_2	0.3 (0.3–0.4)	0.4 (0.3–0.5)	0.4 (0.3–0.4)	0.026

HRF, hypoxic respiratory failure; NHRF, non-hypoxic respiratory failure; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; BT, body temperature; SpO_2, percutaneous oxygen saturation, FiO_2= fraction of inspired oxygen

Vital sign was assessed before initiation of high flow nasal cannula

When we further analyzed the data of the 45 subjects in the failure group, they had their WoSF at a median of 7.1 (3.4–8.9) hours from HFNC application and received rescue management for a median of 22.0 (4.2–72.0) hours thereafter. Specifically, while 17 out of 45 (37.8%) subjects who received HFNC therapy for only ≤24 hours displayed their WoSF at a median of 8.3 (3.4–16.4) hours and progressed into failure 2.2 (0.3–4.3) hours thereafter, the other 28 subjects (62.2%) presented their WoSF at 6.9 (4.0–20.1) hours and went into respiratory failure after 50.4 (24.3–151.4) hours of further management. Regarding WoROX, WoROX–M, and WoROX–Z, those 45 subjects had their worst value at a median of 6.7 (1.6–16.1) hours (for WoROX and ROX–M; and ROX–Z, 6.5 [1.0–14.9] hours) from the HFNC support and finally needed rescue management despite 24.9 (6.4–72.0) hours (for WoROX and ROX–M; and ROX–Z, 24.9 [7.8–73.3] hours) of further application. Among the worst indices of the initial 24 hours, WoSF, and WoROX–M were lower in the HRF group than in the other groups (all $P<0.0166$ in the post–hoc analysis), and WoROX and WoROX–Z were lower in the HRF group than in the success group ($P<0.001$ and $P=0.004$ in the post–hoc analysis, respectively), but not in the NHRF group. SF_{1h}, SF_{3h}, SF_{6h}, SF_{18h}, ROX_{3h}, ROX_{6h}, $ROX–M_{1h}$, $ROX–M_{6h}$, and $ROX–Z_{6h}$ were lower in the HRF group than in the success group ($P<0.0166$ for all indices). The $ROX–M_{3h}$ was lower in the HRF group than in the other groups ($P=0.001$ and $P=0.015$, respectively). SF_{0h}, $ROX–M_{0h}$, and $ROX–Z_{3h}$ showed $P<0.05$, as determined by the Kruskal–Wallis test; however, there were no differences between groups in the post–hoc test (Table 5).

Table 5. Worst respiratory indices during first 1 day of high flow nasal cannula application and all indices at specific times between the success, hypoxic respiratory failure and non-hypoxic respiratory failure groups.

	Success (n=107)	HRF (n=21)	NHRF (n=24)	P
WoSF†	240.0 (199.0-318.3)	166.7 (136.7-181.8)	233.3 (203.2-285.3)	<0.001
WoROX†	5.5 (3.8-7.9)	3.5 (2.6-4.3)	4.6 (3.6-6.6)	0.001
WoROX-M†	155.4 (94.5-216.3)	83.0 (69.0-113.6)	137.7 (113.4-169.4)	0.001
WoROX-Z†	63.9 (30.1-118.3)	25.3 (17.1-68.1)	54.0 (37.2-106.3)	0.009
SF_{0h}§	313.3 (240.0-333.3)	245.0 (192.0-306.7)	281.7 (240.8-326.7)	0.047
SF_{1h}‡	293.3 (235.3-330.0)	193.0 (177.2-242.5)	247.5 (228.2-285.3)	0.001
SF_{3h}‡	303.1 (240.3-333.3)	200.0 (184.0-269.6)	248.8 (227.3-320.0)	0.001
SF_{6h}‡	298.5 (237.8-333.3)	198.0 (188.3-250.2)	250.0 (226.8-303.0)	<0.001
SF_{12h}	287.9 (242.9-333.3)	250.0 (198.0-313.3)	247.5 (220.0-322.1)	0.064
SF_{18h}†	300.3 (237.1-338.7)	226.2 (194.0-277.1)	273.8 (240.0-351.9)	0.024
SF_{24h}	293.9 (236.1-333.3)	240.0 (176.4-286.2)	271.4 (239.0-323.3)	0.059
ROX_{0h}	7.6 (5.3-11.1)	4.6 (3.9-8.8)	5.2 (4.4-10.3)	0.062
ROX_{1h}	6.9 (5.0-10.0)	5.6 (3.9-7.8)	5.3 (4.3-9.7)	0.124
ROX_{3h}‡	7.6 (5.8-10.2)	5.8 (4.4-7.1)	6.4 (4.6-10.1)	0.009
ROX_{6h}†	7.9 (5.7-10.0)	5.8 (4.3-7.8)	6.2 (4.9-8.2)	0.005
ROX_{12h}	8.0 (6.0-10.5)	7.0 (4.6-10.8)	6.5 (5.4-9.8)	0.305
ROX_{18h}	8.0 (5.6-11.2)	5.5 (4.3-11.4)	6.8 (5.8-9.3)	0.315
ROX_{24h}	7.8 (5.6-10.7)	6.2 (4.9-10.5)	7.8 (5.0-9.6)	0.528
$ROX-M_{0h}$§	216.9 (137.4-285.2)	144.6 (94.6-210.9)	172.2 (148.4-300.2)	0.043
$ROX-M_{1h}$†	197.7 (134.1-255.9)	148.7 (91.6-175.4)	189.3 (123.0-246.3)	0.026
$ROX-M_{3h}$†	213.8 (154.3-290.1)	149.4 (104.8-171.8)	184.9 (154.6-294.4)	0.003
$ROX-M_{6h}$‡	220.9 (162.2-292.6)	138.2 (110.8-187.4)	181.7 (147.5-217.5)	0.001
$ROX-M_{12h}$	216.5 (164.5-301.1)	200.5 (129.8-251.0)	210.9 (162.6-230.1)	0.468
$ROX-M_{18h}$	213.7 (156.9-308.0)	160.7 (106.5-255.6)	185.1 (145.6-314.8)	0.109
$ROX-M_{24h}$	216.7 (139.0-292.4)	167.9 (133.9-246.0)	211.9 (160.9-284.0)	0.483
$ROX-Z_{0h}$	111.1 (56.6-379.9)	68.1 (28.0-115.6)	107.1 (62.1-700.4)	0.081
$ROX-Z_{1h}$	115.1 (53.2-311.2)	66.1 (30.3-250.0)	103.9 (39.0-505.7)	0.386
$ROX-Z_{3h}$§	128.5 (63.6-336.8)	65.8 (35.4-145.3)	206.5 (59.9-2491.3)	0.028
$ROX-Z_{6h}$†	199.4 (70.4-576.7)	62.1 (39.0-194.9)	109.8 (59.0-219.9)	0.027

ROX-Z_{12h}	154.9 (71.7-651.7)	141.5 (46.4-6000.0)	108.9 (81.6-3224.3)	0.950
ROX-Z_{18h}	167.5 (72.2-595.4)	131.6 (38.3-427.7)	95.1 (58.3-538.4)	0.575
ROX-Z_{24h}	160.3 (56.3-370.1)	534.6 (52.6-1288.5)	262.1 (83.7-501.4)	0.870

HRF=hypoxic respiratory failure, NHRF=non-hypoxic respiratory failure

Index detected at specific times were described as Index with subscript of time

†The values were significantly lower in the HRF group than in the other two groups in the post-hoc analysis.

‡The values of the HRF group were significantly lower than those of the success group but did not differ from those of the NHRF group in post-hoc analysis.

§There' s no significant difference between two groups in post-hoc analysis.

Table 6 and Figure 2 show the AUC value and best cutoff point for predicting the HRF of each index at different hours. WoSF was a good marker with an AUC of 0.838, which was significantly higher than those for WoROX (0.736), WoROX-M (0.747), and WoROX-Z (0.708) (P=0.039, P=0.043, and P=0.019, respectively).

Table 6. Area under curve to distinguish hypoxic respiratory failure from successful weaning from high flow nasal cannula at each times

	AUC	Sensitivity	Specificity	Cut off value
WoSF	0.838 (0.754-0.921) †	0.810	0.786	197.039
SF_{0h}	0.663 (0.537-0.789) †	0.762	0.496	308.021
SF_{1h}	0.768 (0.651-0.886) †	0.938	0.528	253.205
SF_{3h}	0.749 (0.622-0.875) †	0.632	0.795	230.203
SF_{6h}	0.779 (0.667-0.891) †	0.600	0.876	202.128
SF_{12h}	0.649 (0.512-0.787) †	0.941	0.342	331.667
SF_{18h}	0.700 (0.567-0.833) †	0.611	0.755	238.750
SF_{24h}	0.686 (0.529-0.843) †	0.667	0.653	249.359
WoROX	0.736 (0.625-0.846) †	0.810	0.626	4.533
ROX_{0h}	0.646 (0.508-0.783) †	0.524	0.794	4.673
ROX_{1h}	0.627 (0.484-0.771)	0.500	0.755	4.699
ROX_{3h}	0.711 (0.604-0.818) †	1.000	0.368	8.819
ROX_{6h}	0.671 (0.551-0.790) †	0.950	0.331	9.269
ROX_{12h}	0.546 (0.379-0.713)	0.294	0.865	4.617
ROX_{18h}	0.601 (0.445-0.757)	0.611	0.726	5.691
ROX_{24h}	0.572 (0.398-0.746)	0.600	0.633	6.494
WoROX-M	0.747 (0.632-0.863) †	0.667	0.840	87.283
$ROX-M_{0h}$	0.670 (0.535-0.805) †	0.476	0.870	113.728
$ROX-M_{1h}$	0.707 (0.592-0.821) †	0.875	0.509	191.753
$ROX-M_{3h}$	0.741 (0.633-0.849) †	0.842	0.598	181.684
$ROX-M_{6h}$	0.725 (0.601-0.849) †	0.700	0.744	159.208
$ROX-M_{12h}$	0.562 (0.400-0.724)	0.353	0.856	139.706
$ROX-M_{18h}$	0.652 (0.509-0.795) †	0.500	0.811	145.518
$ROX-M_{24h}$	0.596 (0.429-0.763)	0.667	0.622	186.808
WoROX-Z	0.708 (0.584-0.832) †	0.714	0.687	41.459
$ROX-Z_{0h}$	0.652 (0.516-0.788) †	0.476	0.800	49.378
$ROX-Z_{1h}$	0.606 (0.405-0.763)	0.625	0.632	81.098
$ROX-Z_{3h}$	0.679 (0.547-0.812) †	0.632	0.726	70.280
$ROX-Z_{6h}$	0.651 (0.507-0.796) †	0.500	0.826	53.331
$ROX-Z_{12h}$	0.524 (0.344-0.705)	0.412	0.802	62.554

ROX-Z_{18h}	0.577 (0.424-0.730)	0.389	0.821	54.109
ROX-Z_{24h}	0.473 (0.287-0.659)	0.400	0.745	58.954

AUC; area under the ROC curve

Index detected at specific times were described as index with subscript of time

†p values of area under ROC were below 0.05 in the marked values.

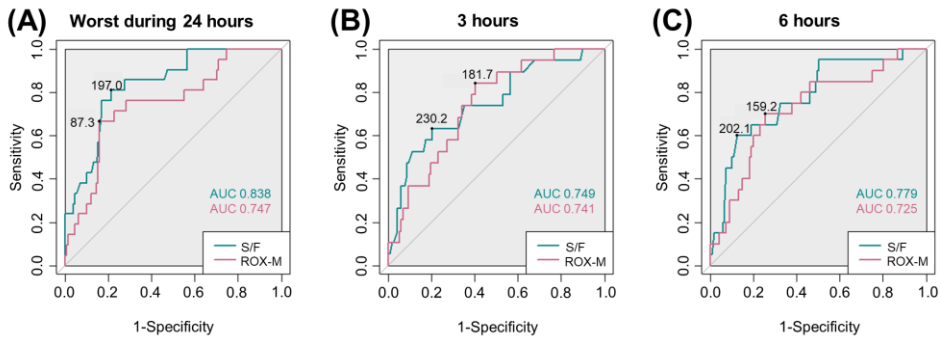

Figure 2. ROC curve of S/F ratio and ROX-M index. (A) The worst S/F ratio and ROX-M index during the first 24 hours after initiation of HFNC (B) ROC curve of index detected at 3 hours and (C) 6 hours after application of HFNC

At each time point, the AUC of S/F was higher than the other indices and the ROX-M was the next highest. The AUC value of S/F was highest when measured at 6 hours compared to other time points, and the remaining indicators were highest at 3 hours. There was no significant difference in the AUC values between S/F and ROX-M measured at 3 hours (P=0.846) and 6 hours (P=0.350) (Figures 2(B, C)). Patients with WoSF smaller than the cutoff value showed high odds ratio than the rest of the patients at 15.63 (95% confidence interval [CI], 4.87-50.20), and the patients with lower SF_{6h} than the cutoff value showed similar odds ratio (OR=18.69; 95%CI, 2.42-144.04) (Table 7).

Risk factors for NHRF were calculated using logistic regression analysis (Table 7). Patients at risk of underweight had an adjusted OR (aOR) of 3.14 (95% CI, 1.22-8.12) and patients with initial hypercapnia ≥65 mmHg had an aOR of 3.26 (95%CI, 1.28-8.31) (Table 7).

Table 7. Univariate and multivariate analysis of predictive factors for high flow nasal cannula failure.

Risk of HRF	Value	Odds ratio	P
WoSF	<197.039	15.63 (4.87-50.20)	<0.001
WoROX-M	<87.283	10.48 (3.78-29.06)	<0.001
SF_{1h}	<253.205	16.8 (2.14-131.79)	<0.001
SF_{3h}	<230.203	6.64 (2.36-18.69)	<0.001
SF_{6h}	<282.128	18.69 (2.42-144.04)	<0.001
Risk of NHRF (Univariate)	Value		P
Underweight		3.45 (1.37-8.67)	0.008
$PvCO_2$ (mmHg)	≥65	3.65 (1.47-9.08)	0.004
Risk of NHRF (Multivariate)			P
Underweight		3.14 (1.22-8.12)	0.018
$PvCO_2$ (mmHg)	≥65	3.26 (1.28-8.31)	0.013

HRF, hypoxic respiratory failure; NHRF, non-hypoxic respiratory failure, $PvCO_2$= venous partial pressure of carbon dioxide

Indices detected at specific times are described as indices with time subscripts.

Comparing the RR measured at each time point between the three groups, there was no significant difference except for the z-score of RR at 3 hours (Table 8).

Table 8. Comparison of respiratory rates and modified the values from each groups

	Success (n=107)	HRF (n=21)	NHRF (n=24)	P
RR_{0h}	40.0 (28.5–52.0)	48.0 (30.0–52.0)	44.0 (31.0–55.0)	0.627
RR_{1h}	40.0 (29.0–50.0)	36.0 (27.5–56.5)	42.0 (32.5–62.0)	0.697
RR_{3h}	36.0 (30.0–48.0)	44.0 (31.0–56.5)	37.0 (30.0–52.0)	0.439
RR_{6h}	36.0 (27.5–47.5)	38.0 (27.5–50.0)	42.0 (35.0–50.0)	0.278
RR_{12h}	36.0 (28.0–48.0)	36.0 (23.0–46.0)	38.0 (32.0–48.0)	0.538
RR_{18h}	36.0 (26.0–48.0)	36.0 (24.0–50.0)	37.0 (34.0–48.0)	0.728
RR_{24h}	36.0 (26.0–48.0)	39.0 (23.5–48.0)	42.0 (32.0–52.0)	0.654
RRM_{0h}	1.5 (1.1–1.8)	1.5 (1.3–2.2)	1.4 (1.1–1.8)	0.273
RRM_{1h}	1.4 (1.1–1.8)	1.5 (1.2–1.9)	1.4 (1.1–2.1)	0.810
RRM_{3h}	1.4 (1.2–1.7)	1.7 (1.4–2.0)	1.2 (1.0–1.8)	0.066
RRM_{6h}	1.3 (1.1–1.6)	1.5 (1.3–2.0)	1.4 (1.2–1.7)	0.192
RRM_{12h}	1.3 (1.1–1.6)	1.4 (0.9–1.8)	1.5 (1.0–1.5)	0.975
RRM_{18h}	1.3 (1.1–1.7)	1.3 (1.1–1.8)	1.5 (1.1–1.7)	0.881
RRM_{24h}	1.3 (1.1–1.8)	1.1 (1.0–1.8)	1.2 (1.1–1.6)	0.839
RRZ_{0h}	2.6 (0.7–5.0)	3.6 (2.1–8.0)	2.4 (0.6–4.5)	0.205
RRZ_{1h}	2.6 (0.9–4.9)	3.6 (1.5–7.0)	1.8 (0.4–7.4)	0.598
RRZ_{3h}	2.3 (1.0–4.7)	4.3 (1.9–5.9)	1.0 (0.1–4.6)	0.048
RRZ_{6h}	1.6 (0.4–3.5)	3.2 (1.6–6.5)	2.4 (1.0–4.3)	0.165
RRZ_{12h}	1.9 (0.5–3.9)	2.3 (-0.7–5.3)	2.9 (0.2–3.1)	0.983
RRZ_{18h}	1.8 (0.4–3.9)	1.8 (0.6–5.3)	2.8 (0.4–4.2)	0.823
RRZ_{24h}	1.9 (0.8–4.6)	0.5 (0.2–4.7)	1.2 (0.6–3.6)	0.834

HRF, hypoxic respiratory failure; NHRF, non-hypoxic respiratory failure; RR, respiratory rate; RRM, respiratory rate/median respiratory rate; RRZ, z-score of respiratory rate

Values detected at specific times were described as values with subscript of time

Chapter 4. Discussion

In this study of 152 pediatric participants, S/F and ROX-M were good early predictors of HRF requiring high levels of respiratory support in patients with HFNC support. WoSF was a good marker with an AUC of 0.838 (0.754-0.921) and SF_{6h} and $ROX-M_{3h}$ were early markers with AUCs of 0.779 (0.667-0.891) and 0.741 (0.633-0.849). Malnutrition with a z-score of weight for age less than -2 and initial increased CO_2 over 65 mmHg were good predictive markers for NHRF, which consisted of airway problems or exacerbation of acidosis.

The results were consistent with those of a previous study on hypoxic respiratory distress, which presented S/F or ROX as predictive markers for HFNC failure (8, 9, 11, 19-21). When the AUC of S/F was compared with ROX or ROX-modified indices in this study, S/F was a better indicator or had a similar diagnostic value, although the index was a simpler form. Comparing the RR measured at each time point between the three groups, there was no significant difference except for the z-score of RR at 3 hours. This may support the fact that these three indices, including another variable, RR, were not superior to S/F. This could be because most of the participants (90.8%) had comorbidities, some of which are known to have tachypnea under mild respiratory failure or even normal conditions; however, an analysis of patients without comorbidities could not be performed due to the small sample size (22, 23).

The indices were markers for only HRF but not for NHRF. As a result of analyzing patients with an oxygen supply of 1 L/min or more before applying HFNC in the data of this study, AUC was higher than the main results of this study in most indices, especially WoSF (0.88) and SF_3 (0.806). The predictability of the index may be high in patients showing early hypoxia. Further studies on

patient populations for which these indices are efficacious will be needed.

Between the original ROX and the other modified indices, there was no significant difference, except that ROX-M showed a better diagnostic value than ROX-Z at 1 hour (P=0.032). The AUC of ROX-M at each time point was higher than that of ROX at the same time point; however, ROX-Z was not always superior to ROX. Based on these results, using the median RR to modify the child's ROX index seems to be a good approach, but the z-score of the RR was not a good option. In a previous study of pediatric acute respiratory failure, ROX-Z measured at 24 hours was shown to be a good predictive marker with an AUC of 0.79 (12). The study included only patients with acute hypoxic respiratory distress with a z-score of RR greater than 2, but only 89 participants (58.2%) from this study met this criterion. Moreover, 10.5% to 21.1% of RR measured at each time point was below the median RR, and ROX-Z in these cases could not reflect the severity of respiratory failure, even though the oxygenation state was poor.

Several studies for children presented ROX or ROX-HR (ratio of ROX by heart rate), without modification considering age, as a predictive index of HFNC failure, with AUC from 0.717 to 0.81(24, 25, 26). They included a specific age group under 24 months or median age below 12 months, and these indices are not suitable for whole pediatric patients, considering ROX-M showed higher AUC than ROX in this study. Additionally, modified RR considering baseline RR can be devised as a better index than ROX-M and ROX-Z since RR is affected by the patient's chronic respiratory failure status and age. We did not perform the analysis using baseline RR because we could not collect the data, especially in the failure group. Further studies are needed to confirm the index using baseline RR as a predictive marker.

ROX-HR was another index presented in several studies.

ROX-HR at 2 hours and POX-HR (substitution of SpO_2 to PaO_2 in ROX-HR) at 3.33 hours in adult studies and ROX-HR at 6 hours in children under 24 months of age have been suggested as predictable markers (24, 27, 28). Further analysis of the ROX-HR from data of this study showed the highest AUC of 0.724 for the ROX-HR at 3 hours, which was lower than AUC of SF_6 or ROX-M_3. Further research will be needed to determine if an index using heart rate is preferable in children.

In this study, we assessed the significance of evaluating the worst within-24-hours indices after initiating HFNC therapy. When we carefully examined the period between the worst within-24-hours values were determined and the rescue managements were applied, there was a median of at least 22 hours. Moreover, for those 28 subjects who reached HFNC failure after 24 hours of HFNC application, the period extended to around 50 hours (for WoSF and WoROX-M, a median of 50.4 and 51.3 hours, respectively). Furthermore, the worst within-24-hours indices below a certain cutoff substantially elevate the risk of HRF. Therefore, we can consider using these indices to prevent belated rescue management by identifying subjects in impending HRF. Efficacy was maximized in the group that received HFNC therapy for more than 24 hours, while it was lower in those who received rescue management earlier. For these patients, SF1, SF3, and SF6 could be more useful indices for early detection. If these indices are below the cut-off value, the patients can be predicted to be at risk of rescue management. In the patients who were supported with HFNC for more than 24 hours, if the worst indices during the previous 24 hours are below the cut-off value, the patients are also at risk of HRF.

When it comes to the NHRF, malnutrition and initial hypercapnia were independent risk factors for NHRF. In a previous study of children with pneumonia, underweight patients tended to require oxygen and had longer mechanical ventilation periods (29).

Respiratory muscle fatigue is a major problem in children with respiratory distress due to the anatomical characteristics of the chest wall and diaphragm. Malnutrition can be attributed to respiratory failure as the condition can decrease the threshold of fatigue due to poor energy reserves (30). In addition, malnutrition adversely affects the maturation of surfactants and respiratory muscle and elastic fibers according to previous animal study, which can impair respiratory function in malnourished patients (31).

This study had several limitations owing to its retrospective study design. First, this study did not present the arterial blood gas results. Some studies have suggested a new indicator replacing SpO_2 with PaO_2 in ROX as a better indicator than ROX to predict HFNC failure (27, 28). In general wards, practically, SpO_2 is monitored as a substitute for PaO_2 and $PvCO_2$ as one for $PaCO_2$ because of the difficulty of repetitive arterial blood sampling in children, especially outside the intensive care unit. Although we did not directly measure PaO_2, a prerequisite for diagnosing hypoxemia, the ratio of SpO_2 to FiO_2 is known to correlate with the ratio of $PaCO_2$ to FiO_2 (19). Furthermore, $PaCO_2$ is well associated with $PvCO_2$ (32, 33). Indices requiring arterial blood sampling for patients in the ward may be less preferred than in the intensive care unit. Second, the study has the potential for misclassification bias because the decision of intubation was made by the judgment of the clinician, and at times, the decision could be made before hypoxia occurs. However, in patients classified as NHRF, other intubation criteria were fulfilled, reflecting the actual clinical situation. Third, the flow rate of the HFNC was not taken into account, even though higher flow rates can increase the ROX by decreasing RR of the patient (10). However, there was no difference in the initial flow rate per body weight between the groups (Table 4), and it is unlikely that the flow rate would be reduced within 6 hours, resulting in a small effect of flow. Finally, patients in the NHRF group may not be supported by a sufficient flow rate because they are more prone to malnutrition, and the

range of flow rate was set according to body weight. In an additional analysis using the ideal body weight based on the patient's age and height, there was no difference in the flow rate divided by the ideal body weight. Therefore, there was no evidence of an insufficient flow rate in the NHRF group. However, further studies are needed to determine the extent of sufficient flow in patients with malnutrition (34).

HRF and NHRF patients showed different characteristics of respiratory index and nutrition status. The respiratory indices presented in this study were good predictors for HRF but did not differentiate NHRF from the success group. Hypercapnia and respiratory distress such as severe tachypnea and chest retraction are also important indications for HFNC, and they can be mixed with hypoxia during the initial stage of respiratory failure (6, 35). Therefore, assessing the risk of both HRF and NHRF in patients in need of HFNC supplies helps in rapid decision-making.

This is the first study to predict HFNC failure in pediatric patients with respiratory distress, including various type of respiratory failure requiring HFNC. In addition, this study was conducted on patients mainly in the ward (63.2%) and emergency room (20.4%), unlike previous studies in intensive care unit. The indices from this study could be used to detect HFNC failure early in ward and emergency room and determine allocation of medical resources such as intensive care unit. S/F and ROX-M are good early indicators for predicting HRF in pediatric patients, but cannot predict the failure with other causes. Malnutrition with a weight for age below -2 SD and initial hypercapnia over 65 mmHg are risk factors for NHRF. For these patients, an inspection of respiration and frequent evaluation of acidosis are required to avoid intubation delays.

Chapter 5. Conclusion

For pediatric respiratory distress, S/F and ROX-M can be used for early prediction of hypoxic HFNC failure. Patients with malnutrition or hypercapnia are at high risk and should be considered for intubation other than oxygen demand.

Bibliography

1. Helviz Y, Einav S. A Systematic review of the high-flow nasal cannula for adult patients. Crit Care. 2018;22(1):71.
2. Benaron DA, Benitz WE. Maximizing the stability of oxygen delivered via nasal cannula. Arch Pediatr Adolesc Med. 1994;148(3):294- 300.
3. Sztrymf B, Messika J, Bertrand F, Hurel D, Leon R, Dreyfuss D, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med. 2011;37(11):1780- 6.
4. Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth. 2011;107(6):998 - 1004.
5. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185- 96.
6. Lee HW, Choi SM, Lee J, Park YS, Lee CH, Yoo CG, et al. Reduction of PaCO2 by high-flow nasal cannula in acute hypercapnic respiratory failure patients receiving conventional oxygen therapy. Acute Crit Care. 2019;34(3):202- 11.
7. Kang BJ, Koh Y, Lim CM, Huh JW, Baek S, Han M, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. 2015;41(4):623- 32.
8. Roca O, Messika J, Caralt B, Garcia-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The

utility of the ROX index. J Crit Care. 2016;35:200- 5.
9. Chandel A, Patolia S, Brown AW, Collins AC, Sahjwani D, Khangoora V, et al. High-flow nasal cannula therapy in COVID-19: Using the ROX index to predict success. Respir Care. 2021;66(6):909- 19.
10. Mauri T, Carlesso E, Spinelli E, Turrini C, Corte FD, Russo R, et al. Increasing support by nasal high flow acutely modifies the ROX index in hypoxemic patients: A physiologic study. J Crit Care. 2019;53:183- 5.
11. Mellado-Artigas R, Mujica LE, Ruiz ML, Ferreyro BL, Angriman F, Arruti E, et al. Predictors of failure with high-flow nasal oxygen therapy in COVID-19 patients with acute respiratory failure: a multicenter observational study. J Intensive Care. 2021;9(1):23.
12. Yildizdas D, Yontem A, Iplik G, Horoz OO, Ekinci F. Predicting nasal high-flow therapy failure by pediatric respiratory rate-oxygenation index and pediatric respiratory rate-oxygenation index variation in children. Eur J Pediatr. 2021;180(4):1099-106.
13. WHO Multicentre Growth Reference Study Group. WHO child growth standards based on length/height, weight and age. Acta Paediatr Suppl. 2006;450:76- 85.
14. Kim JH, Yun S, Hwang SS, Shim JO, Chae HW, Lee YJ, et al. The 2017 Korean national growth charts for children and adolescents: development, improvement, and prospects. Korean J Pediatr. 2018;61(5):135- 49.
15. WHO Multicentre Growth Reference Study Group. Comparison of the World Health Organization (WHO) child growth standards and the national center for health statistics/WHO international

growth reference: implications for child health programmes. Public Health Nutr. 2006;9(7):942- 7.
16. Kreit JW. Mechanical ventilation: physiology and practice. 2nd, editor: Oxford University Press; 2017.
17. Schonhofer B, Kuhlen R, Neumann P, Westhoff M, Berndt C, Sitter H. Clinical practice guideline: non-invasive mechanical ventilation as treatment of acute respiratory failure. Dtsch Arztebl Int. 2008;105(24):424- 33.
18. Bae W, Kim K, Lee B. Distribution of pediatric vital signs in the emergency department: a nationwide study. Children (Basel). 2020;7(8):89.
19. Kim GE, Choi SH, Park M, Jung JH, Lee M, Kim SY, et al. SpO2/FiO2 as a predictor of high flow nasal cannula outcomes in children with acute hypoxemic respiratory failure. Sci Rep. 2021;11(1):13439.
20. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernandez G, 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(11):1368- 76.
21. Ferrer S, Sancho J, Bocigas I, Bures E, Mora H, Monclou E, et al. ROX index as predictor of high flow nasal cannula therapy success in acute respiratory failure due to SARS-CoV-2. Respir Med. 2021;189:106638.
22. Pfeffer G, Povitz M, Gibson GJ, Chinnery PF. Diagnosis of muscle diseases presenting with early respiratory failure. J Neurol. 2015;262(5):1101- 14.
23. Ross RD. Grading the graders of congestive heart failure in children. J Pediatr. 2001;138(5):618- 20.
24. Webb LV, Chahine R, Aban I, Prabhakaran P, Loberger JM.

Predicting high-flow nasal cannula therapy outcomes using the ROX-HR index in the pediatric ICU. Respir Care. 2022; DOI: https://doi.org/10.4187/respcare.09765

25. Kannikeswaran N, Whittaker P, Sethuraman U. Association between respiratory rate oxygenation index and need for positive pressure ventilation in children on high flow nasal cannula for bronchiolitis. Eur J Pediatr. 2022, 181 (11):3977-83.
26. Liu J, Li D, Luo L, Liu Z, Li X, Qiao L. Analysis of risk factors for the failure of respiratory support with high-flow nasal cannula oxygen therapy in children with acute respiratory dysfunction: A case-control study. Front Pediatr. 2022;10:979944.
27. Li Z, Chen C, Tan Z, Yao Y, Xing S, Li Y, et al. Prediction of high-flow nasal cannula outcomes at the early phase using the modified respiratory rate oxygenation index. BMC Pulm Med. 2022;22(1):227.
28. Kansal A, Ong WJD, Dhanvijay S, Siosana ATP, Padillo LM, Tan CK, et al. Comparison of ROX index (SpO2/FIO2 ratio/respiratory rate) with a modified dynamic index incorporating PaO2/FIO2 ratio and heart rate to predict high flow nasal cannula outcomes among patients with acute respiratory failure: a single centre retrospective study. BMC Pulm Med. 2022;22(1):350.
29. Johar D, Day AG, Ziegler EE. Clinical presentation of malnourished patients with pneumonia requiring prolonged ventilatory support. Int J Clin Pediatr. 2016;5(2):19- 28.
30. Gea J, Sancho-Munoz A, Chalela R. Nutritional status and muscle dysfunction in chronic respiratory diseases: stable

phase versus acute exacerbations. J Thorac Dis. 2018;10(Suppl 12):S1332- S54.

31. Dias CM, Passaro CP, Cagido VR, Einicker-Lamas M, Lowe J, Negri EM, et al. Effects of undernutrition on respiratory mechanics and lung parenchyma remodeling. J Appl Physiol (1985). 2004;97(5):1888- 96.
32. Chu YC, Chen CZ, Lee CH, Chen CW, Chang HY, Hsiue TR. Prediction of arterial blood gas values from venous blood gas values in patients with acute respiratory failure receiving mechanical ventilation. J Formos Med Assoc. 2003;102(8):539 - 43.
33. Malatesha G, Singh NK, Bharija A, Rehani B, Goel A. Comparison of arterial and venous pH, bicarbonate, PCO2 and PO2 in initial emergency department assessment. Emerg Med J. 2007;24(8):569- 71.
34. Ward SL, Quinn CM, Steurer MA, Liu KD, Flori HR, Matthay MA. Variability in pediatric ideal body weight calculation: implications for lung protective mechanical ventilation strategies in pediatric acute respiratory distress syndrome. Pediatr Crit Care Me 2018;19(12):e643.
35. Yuste ME, Moreno O, Narbona S, Acosta F, Penas L, Colmenero M. Efficacy and safety of high-flow nasal cannula oxygen therapy in moderate acute hypercapnic respiratory failure. Rev Bras Ter Intensiva. 2019;31(2):156- 63.

요약 (국문초록)

고유량비강캐뉼라를 적용하는 소아 환자에서 비침습적 지표를 이용한 호흡부전 경과 예측에 대한 연구

연구배경: 고유량비강캐뉼라는 호흡부전 소아에서 유용한 호흡 보조 장치이지만 기관 삽관과 같은 침습적 기도 확보의 시점을 늦출 수 있다고 알려져 있다. 최근에는 고유량비강캐뉼라의 실패를 조기에 예측하기 위해 경피적 산소 포화도, 산소분압과 호흡수를 이용한 여러 지표가 제시되어 왔다. 본 연구는 고유량비강캐뉼라를 적용하는 환자에서 호흡부전을 예측하기 위한 다양한 비침습적 지표를 평가하고자 하였다.

연구방법: 고유량비강캐뉼라에서 추가 호흡 보조를 필요로 했던 환자들은 기관삽관의 원인에 따라 hypoxic respiratory failure (HRF)와 non-HRF (NHRF)로 분류되었다. 경피적 산소포화도를 산소분율로 나눈 비(S/F), S/F를 RR로 나눈 비 (ROX), S/F를 호흡수의 중간값 대비 환자의 호흡수로 나눈 비 (ROX-M), S/F를 환자 호흡수의 z score로 나눈 비를 계산하여 지표로서의 가치를 비교하였다. 고유량비강캐뉼라는 제거한 군, HRF, NHRF 군 사이에 나타난 각 지표의 차이를 비교하였다.

연구결과: 152명의 증례를 수집하였는데 이중 45명(29.6%0)는 고유량비강캐뉼라를 제거하지 못하였다. 이 중 21명(46.7%)는 HRF에 속하였고, 24명(53.3%)는 NHRF였다. 3시간과 6시간에 측정된 S/F와 ROX-M 값은 높은 AUC 값을 보여 각각 HRF를 예측하는 좋은 지표로 제시되었다. 반면 초기의 고탄산혈증과 저체중이 각각 NHRF의 위험 요소로 제시되었다.

결론: 고유량비강캐뉼라를 적용하는 소아에서 기관삽관을 조기에 결정하

는데 있어 65mmHg 이상의 고탄산혈증 유무와 저체중 여부, 그리고 S/F, ROX-M 등을 모니터하는 것은 유용한 예측 지표로 사용될 수 있다.

주요어 : 고유량비강캐뉼라, 소아호흡부전, 위험 요소, ROX 지표, S/F 비
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