Predicting High-Flow Nasal Cannula Therapy Outcomes Using the ROX-HR Index in the Pediatric ICU

Lece V Webb, Rouba Chahine, Inmaculada Aban, Priya Prabhakaran, and Jeremy M Loberger

BACKGROUND: High-flow nasal cannula (HFNC) use is increasing in pediatric patients. Objective measures that predict HFNC outcomes are lacking. The respiratory rate-oxygenation (ROX) and ROX heart rate (ROX-HR) indices are validated to predict HFNC therapy failure in adults. This study examined the performance of both indices in predicting HFNC therapy failure in children admitted to the pediatric ICU (PICU). METHODS: This retrospective, longitudinal, observational cohort study was completed in a 24-bed PICU in a quaternary care children's hospital. All subjects ≤ 24 months of age initiated on HFNC in the PICU from January 1, 2018–August 31, 2020, were included. The ROX and ROX-HR indices were collected at standardized time points during HFNC therapy. Performance in predicting HFNC failure was evaluated using area under the receiver operating characteristic curve (AUROC) and Kaplan-Meier survival analysis. Failure was defined as escalation of respiratory support to either noninvasive ventilation or endotracheal intubation. RESULTS: Among 446 subject encounters, 111 (24.9%) failed HFNC therapy. HFNC failure was associated with lower ROX and ROX-HR indices at termination compared to HFNC liberation ($P < .001$). A ROX-HR index < 3 was significantly associated with a higher risk of HFNC failure at 1 (AUROC 0.76, $P = .01$) and 6 (AUROC 0.81, $P = .02$) h. CONCLUSIONS: ROX-HR may be a useful tool for early identification of patients ≤ 24 months at risk for HFNC failure and allow for earlier intervention. Larger prospective studies are necessary to validate the utility of the ROX-HR index in pediatric patients. *Key words: pediatrics; critical care; bronchiolitis; noninvasive ventilation; respiratory insufficiency; high-flow nasal cannula.* [Respir Care 2022;67(11):1377–1384. © 2022 Daedalus Enterprises]

Introduction

High-flow nasal cannula (HFNC) use in children is increasing and is associated with a reduction in both intubation rates and mortality.[1-5] HFNC is an enticing alternative to conventional noninvasive ventilation as it is well tolerated and has been associated with improvements in dead-space washout, lung compliance, mucociliary clearance, and work of breathing.[6-9] However, a major evidence gap exists in the assessment of response to and prediction of failure of this emerging therapy. The result is excessive reliance on subjective biases of health care providers leading to variability in practice and outcome. Escalation to invasive mechanical ventilation is accompanied by significant morbidity and mortality.[10-12] However, similar complications are associated with delayed intubation.[13-15] Therefore, it is imperative to identify objective predictors to aid in the early identification of and intervention in patients at risk for HFNC failure.

Breathing frequency, heart rate, work of breathing, and oxygenation are routinely used to monitor patients on HFNC therapy. Vital signs lack standardized thresholds for predicting HFNC outcomes. The work-of-breathing assessment is highly subjective in the absence of advanced monitoring such as esophageal manometry or respiratory inductance plethysmography.[16] The respiratory rate-

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oxygenation (ROX) and ROX heart rate (ROX-HR) indices have been validated to predict HFNC outcomes in adult patients with pneumonia and acute respiratory failure, with lower scores predicting higher risk for HFNC failure (Fig. 1).[5,17-18] Positive predictors of HFNC success are located in the numerator, whereas negative predictors are located in the denominator. These indices have not been studied in critically ill children as an objective measure to predict HFNC outcomes in children. The objective of this study was to evaluate the predictive utility of the ROX and ROX-HR indices for HFNC failure in critically ill children ≤ 24 months initiated on HFNC as either initial respiratory support or as postextubation respiratory support.

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QUICK LOOK

Current knowledge

The respiratory rate-oxygenation (ROX) and ROX heart rate (ROX-HR) indices are validated objective measures to predict high-flow nasal cannula (HFNC) failure in adults. However, there is not currently a standardized objective measure to predict HFNC failure in children. Heart rate is a useful early predictor in children who respond to HFNC therapy, but clinical studies have not explored the utility of ROX-HR index.

What this paper contributes to our knowledge

A ROX-HR index < 3 at 1 h and 6 h of HFNC use correlated with a high risk of HFNC failure and the need for escalation of care. Therefore, the ROX-HR may be a useful tool for early identification of HFNC failure in patients ≤ 24 months old.

Methods

Study Setting

The study was conducted in a 24-bed medical-surgical pediatric ICU (PICU) within a quaternary-care academic children's hospital. There is a separate cardiovascular ICU and step-down unit. There was no established standard protocol for HFNC therapy initiation, titration, or discontinuation in the PICU during the study period. The prescriber dictated HFNC management. This study was approved by the local institutional review board (IRB-30005877), and the need for informed consent was waived.

Study Design

This was a retrospective, longitudinal, observational cohort study of all patient encounters ≤ 24 months of age treated with HFNC in the PICU from January 1, 2018–August 31, 2020. Encounters were identified using the institutional data within the Virtual Pediatric Intensive Care Systems, LLC database. Encounters generated by this report were manually verified, and all data elements were manually abstracted from the electronic medical record by the principal investigator. In cases of ambiguity created by retrospective data collection, informal adjudication occurred among investigators.

Patient encounters with a home oxygen requirement, any relative contraindication to noninvasive ventilation (NIV) (eg, craniofacial abnormalities, craniofacial trauma), intubation for diagnostic or therapeutic planned procedures, < 7 days between HFNC encounters, and patients who had any order for limitations of care (eg, do not resuscitate) were excluded from the study. Multiple HFNC encounters for the same subject were permitted if all criteria above were met.

Data Elements and Definitions

HFNC use was defined as the use of the Optiflow or Optiflow Junior device for delivery of heated humidified oxygen (Fisher & Paykel Healthcare, Auckland, New Zealand). Indications for HFNC therapy were either initial respiratory support or postextubation respiratory support. Descriptive data elements collected included subject age, sex, race, and comorbid conditions (presence of a genetic/syndromic condition, chronic neurologic disorder, chronic respiratory disorder, and prematurity). Clinical data elements collected included the Pediatric Index of Mortality 3 (PIM-3) scores, HFNC duration, maximum flows, PICU and hospital length of stay (LOS), and mortality.

The primary outcome was HFNC failure. HFNC failure was defined as escalation of respiratory support either to NIV or invasive mechanical ventilation. HFNC success was defined as liberation from HFNC without escalation NIV or intubation at any point. The ROX and ROX-HR indices were calculated before initiation of HFNC and at 1, 2, 4, 6, 8, 10, 12, 18, 24, and 48 h after HFNC initiation. At

Example of ROX index calculation:

$S_{pO_2} / [F_{IO_2} \times f]$

$95 / [0.5 \times 25] = 7.6$

Example of ROX-HR index calculation:

$[S_{pO_2} \times 100] / [F_{IO_2} \times f \times HR]$

$[95 \times 100] / [0.5 \times 25 \times 120] = 6.3$

Pulse oximetry (S_{pO_2}) – 95%
Fraction of inspired oxygen (F_{IO_2}) – 0.5
Frequency (f, breaths/min) – 25
Heart rate (HR, beats/min) – 120

Fig. 1. Example calculation of the respiratory rate-oxygenation (ROX) index and ROX heart rate (ROX-HR) index.

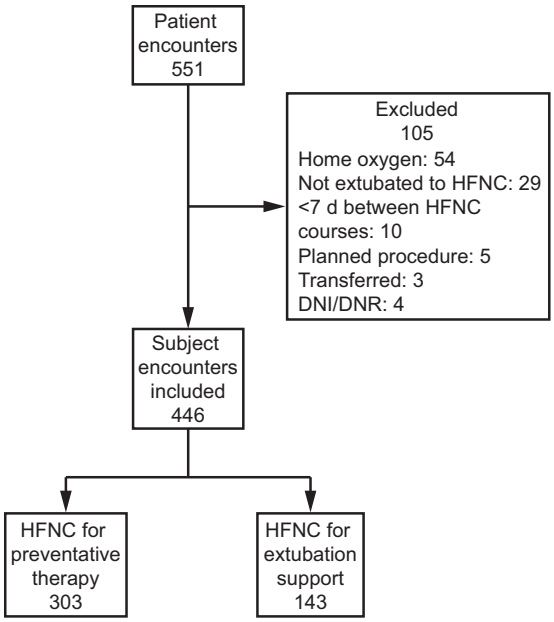

Fig. 2. Flow chart. HFNC = high-flow nasal cannula; DNI/DN = do not intubate/do not resuscitate.

the time of termination of HFNC, the ROX and ROX-HR indices were calculated using the latest parameters available before termination.

Statistical Analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). Subjects successfully liberated from HFNC were compared to those who failed HFNC. The data are expressed as frequencies (%) for categorical variables and as mean (SD) or median (interquartile range [IQR]) for continuous variables. When appropriate, *t* test or Wilcoxon test was used to compare continuous variables between groups. Chi-square or Fisher exact tests were used to compare categorical variables. The ROX and ROX-HR indices were analyzed at different time points using logistic regression to determine which time point was most predictive of failure. The area under the curve receiver operating characteristic (AUROC) curves was obtained in addition to the *P* values for testing the strength of the association of the ROX and ROX-HR at a given time point with the outcome. The optimal cutoff was determined for the ROX and ROX-HR indices using the Youden J index based on maximizing the sum of sensitivity and specificity as a starting point. Given our interest in identifying patients with the highest risk of HFNC failure as early as possible, the final cutoffs were determined by maximizing sensitivity with consideration of specificity and practical clinical issues. Kaplan-Meier plots for HFNC failure were developed from the chosen cutoff. Multivariate cox proportional regression analysis was performed to estimate the probability of HFNC failure based on categorized ROX-HR index based on cutoff. The model was adjusted for PIM-3 score and race. As an exploratory analysis, Cox proportional models were fitted stratified by age group to examine if the results would differ by age subgroup. All hypotheses tests were 2-tailed, and a *P* value $\leq .05$ was considered significant.

Results

Subject Population and Outcomes

The study CONSORT diagram is presented in Figure 2. There were 446 subject encounters included, representing 361 unique subjects. HFNC was more commonly deployed as initial respiratory support (67.9%) compared to postextubation support (32.1%). Table 1 shows the descriptive data elements and outcome results. Bronchiolitis was the most common primary diagnosis (75.8%). The cohort HFNC failure rate was 24.9% at a median of 8.3 (IQR 3.0–17.6) h after HFNC initiation. The failure rate in subjects < 12 months old was 25.3%. Of the subjects who failed HFNC, 36.9% required NIV, 53.2% required intubation, and 9.9% required both. In univariate analysis, HFNC failure was associated with a higher PIM-3 score at admission ($P < .001$) and non–white race ($P = .02$). There were higher median flows ($P < .001$) and max F_{IO_2} ($P = .003$) in subjects who failed HFNC. HFNC failure was associated with longer PICU LOS ($P < .001$), hospital LOS ($P < .001$), and mortality ($P = .004$).

Performance of the ROX and ROX-HR Indices

Subjects who failed HFNC, regardless of indication, had significantly lower ROX and ROX-HR scores at termination of HFNC compared to those liberated from HFNC ($P < .001$). ROX-HR index was a stronger predictor of outcome based on AUROC and *P* value relative to the ROX index (Table 2). The ROX-HR index at 1 h was a significant predictor of HFNC failure at 2, 6, 8, and 10 h. The ROX-HR index at 1 h predicted HFNC failure at 2 h with a sensitivity of 90% and specificity of 52% (AUROC 0.76, $P = .01$). Among those who failed HFNC therapy, there was no significant difference between the baseline ROX-HR index and the ROX-HR index 1 h post initiation when compared to those who were successfully liberated from HFNC. The ROX-HR index at 6 h was also a significant predictor of HFNC failure at 8 and 10 h. The ROX-HR index at hour 6 predicted HFNC failure at 8 h with a sensitivity 71% and specificity 92% (AUROC 0.81, $P = .02$). Using the 1 h and 6 h ROC curves (Fig. 3), the failure prediction cutoffs for the ROX-HR index were determined to be 3.5 and 2.7, respectively. Survival analysis using Kaplan-Meier plots was evaluated using a cutoff of < 3.0

Table 1. Descriptive Characteristics and Outcomes Measures for All Subjects Treated With High-Flow Nasal Cannula

Descriptive Variable or Outcome Measure (no. = 446)	HFNC Success	HFNC Failure	*P*
Encounters, no. (%)	335 (75.1)	111 (24.9)	
Median age, months (IQR)	7 (2–14)	5 (2–13)	.30
Male, *n* (%)	191 (57)	66 (59.5)	.65
Race, *n* (%)			
White	169 (50.4)	42 (37.8)	.02
Non-white*	164 (49)	69 (62.2)	
Primary diagnosis, *n* (%)			
Bronchiolitis	252 (75.2)	86 (77.5)	.63
Non-bronchiolitis respiratory process	83 (24.8)	25 (22.5)	
Comorbidities, *n* (%)			
Genetic syndrome	17 (5.1)	10 (9)	.13
Neurologic	27 (8.1)	7 (6.3)	.55
Respiratory	34 (10.1)	9 (8.1)	.53
Prematurity†	103 (30.7)	38 (34.2)	.45
Initial respiratory support, *n* (%)	213 (63.6)	90 (81.1)	< .001
Postextubation respiratory support, *n* (%)	122 (36.4)	21 (18.9)	
Median PIM-3 ROM score (IQR)	0.28 (0.22–0.93)	0.92 (0.24–1.00)	< .001
Median HFNC duration, h (IQR)	31.5 (17.5–56.7)	8.3 (3.0–17.6)	< .001
Mean max flow, L/kg/min (SD)	1.5 (0.5)	1.7 (0.5)	< .001
Median max F_{IO_2} (IQR)	0.5 (0.4–0.7)	0.5 (0.5–1.0)	.003
Median ROX at HFNC termination‡ (IQR)	6.5 (4.9–9.1)	3.5 (2.0–4.5)	< .001
Median ROX-HR at HFNC termination‡ (IQR)	4.7 (3.4–7.3)	2.2 (1.3–3.1)	< .001
Median PICU LOS, d (IQR)	2.2 (1.0–4.3)	4.7 (2.5–9.5)	< .001
Median hospital LOS, d (IQR)	5.8 (2.9–11.5)	10.3 (5.3–20.7)	< .001
Mortality, *n* (%)	0	4 (3.6)	.004

Data are presented as *n* (%), median (interquartile range), or mean (SD).
* $n = 3$ in success cohort excluded due to unavailable race data.
† $n = 9$ in success and $n = 4$ in failure cohorts excluded due to unavailable gestation data.
‡ $n = 1$ in success and $n = 1$ in failure cohorts excluded due to unavailable data at HFNC termination.
HFNC = high-flow nasal cannula
PIM-3 ROM = Pediatric Index of Mortality 3 risk of mortality
ROX = respiratory rate-oxygenation index
ROX-HR = ROX heart rate index
PICU = pediatric ICU
LOS = length of stay

and < 3.5 at these time points. The cutoff of < 3 was more significant at both 1 ($P = .005$) and 6 h ($P = .048$) (Fig. 4). In multivariate Cox proportional hazard analysis including PIM-3 score, race, and ROX-HR index, only non–white race ($P = .041$) and ROX-HR ($P = .008$) were significantly associated with HFNC failure.

Exploratory Age-Based Analysis

Subjects were evaluated in following age groups: < 6 months, 6–12 months, and > 12 months. Among subjects < 6 months of age, ROX-HR was significantly associated with HFNC failure ($P = .009$) after multivariate analysis including PIM-3 score, race, and ROX-HR. ROX-HR was not significantly associated with HFNC in the other age groups.

Discussion

ROX-HR index may be a helpful tool to identify children ≤ 24 months old who are at increased risk for HFNC failure. Importantly, this identification may occur as soon as 1 h with good sensitivity for failure within the next hour. A ROX-HR cutoff < 3 was significantly associated with a higher risk of HFNC failure at both 1 and 6 h. In multivariate analysis, both ROX-HR index and race (white vs non-white) were associated with HFNC failure, suggesting social determinants of health may play a role in HFNC outcomes.

Delayed intubation is associated with increased morbidity and mortality.[13-15] However, selection and timing of escalation of care remain a major clinical challenge. In critically ill patients, identifying patients at high risk quickly after HFNC initiation can facilitate earlier

Table 2. Prediction of High-Flow Nasal Cannula Success Based on Respiratory Rate-Oxygenation Index and Respiratory Rate-Oxygenation Heart Rate Index Cutoffs at Different Time Points

	ROX	*P*	AUROC	Cutoff	Sensitivity	Specificity	J Index	no.
HFNC at 2 h	Hour 1 ROX	.040	0.69	3.76	0.45	0.92	0.38	401
HFNC at 2 h	Hour 1 ROX-HR	.01	0.76	3.53	0.90	0.52	0.42	392
HFNC at 6 h	Hour 1 ROX	.01	0.63	6.41	0.83	0.42	0.25	401
HFNC at 6 h	Hour1 ROX-HR	.004	0.68	3.68	0.83	0.50	0.33	392
HFNC at 8 h	Hour 1 ROX	.002	0.65	6.41	0.82	0.42	0.24	401
HFNC at 8 h	Hour 1 ROX-HR	.001	0.70	3.26	0.70	0.63	0.33	392
HFNC at 10 h	Hour 1 ROX	.003	0.63	6.41	0.79	0.42	0.21	401
HFNC at 10 h	Hour1 ROX-HR	.001	0.67	4.04	0.80	0.47	0.28	392
HFNC at 6 h	Hour 4 ROX	.19	0.69	7.27	1.00	0.42	0.42	386
HFNC at 6 h	Hour 4 ROX-HR	.18	0.71	4.69	1.00	0.44	0.44	385
HFNC at 8 h	Hour 4 ROX	.004	0.77	4.42	0.54	0.91	0.44	386
HFNC at 8 h	Hour 4 ROX-HR	.006	0.77	2.66	0.62	0.87	0.48	385
HFNC at 10 h	Hour 4 ROX	.003	0.71	7.44	0.95	0.42	0.37	396
HFNC at 10 h	Hour 4 ROX-HR	.002	0.73	5.38	1.00	0.40	0.40	385
HFNC at 8 h	Hour 6 ROX	.02	0.78	5.08	0.71	0.85	0.57	369
HFNC at 8 h	Hour 6 ROX-HR	.02	0.81	2.70	0.71	0.92	0.64	369
HFNC at 10 h	Hour 6 ROX	.001	0.72	5.05	0.53	0.84	0.38	369
HFNC at 10 h	Hour 6 ROX-HR	.007	0.74	3.24	0.60	0.78	0.38	369
HFNC at 10 h	Hour 8 ROX	.02	0.79	6.60	0.88	0.66	0.54	354
HFNC at 10 h	Hour 8 ROX-HR	.02	0.78	4.34	0.88	0.63	0.51	353

ROX = respiratory rate-oxygenation index
AUROC = area under the receiver operating characteristic curve
HFNC = high-flow nasal cannula
ROX-HR = ROX heart rate index

intervention and potentially mitigate morbidity and mortality. The 1-h ROX-HR score predicts failure at 2 h with good sensitivity (90%), limiting false HFNC success predictions and inappropriate delays in care. However, attention to poor specificity (52%) is necessary, which could lead to false failure predictions and inappropriate escalation of care. At 6 h, the sensitivity of the ROX-HR score for HFNC failure by 8 h is less (71%), likely due in part to dropout of subjects that have already failed (median failure time, 8.3 h), which can affect the sensitivity in either direction, but has decreased in the case. However, the specificity is dramatically improved (92%), lessening the likelihood of inappropriate escalation of care at this time point. Therefore, a ROX-HR index < 3 at 1 h is highly sensitive for HFNC failure, whereas the same index is more specific at 6 h. The most important clinical application is likely the sensitive, early identification of patients requiring escalation of care in the first 2 h of HFNC use.

A recently published pediatric study investigating both the ROX index and variation in ROX index as markers for HFNC failure found that these indices can predict failure at 24 and 48 h.[19] Whereas this was an instructive and well-conceived study, it has several limitations. First, it included all subjects from 1 month–18 y old in a variety of settings (emergency department, pediatric wards, and PICU).[19] HFNC use has been most rigorously studied in children $\leq$ 24 months of age. Furthermore, the illness severity is highly variable across these different care environments. In our study, only the sickest children (as evidenced by their PICU admission requirement) and $\leq$ 24 months of age were included. The median duration of HFNC at failure was much longer in the Yildizas et al study (19.2 h vs 8.3 h). Additionally, predictive performance was maximal at 2 d versus 1 and 6 h in our study.[19] Our results suggest improved performance in early identification of patients at highest risk of failure. Lastly, the ROX-HR index was not evaluated. Heart rate is an integral part of the pediatric assessment and can provide early signs of clinical deterioration.[20] It has been previously established that heart rate is a useful early predictor in children who respond to HFNC therapy.[21-23] Sochet et al showed a significant reduction in heart rate in HFNC responders $\leq$ 24 months old within 1 h of HFNC initiation, whereas nonresponders had no observable differences in heart rate.[23] This knowledge coupled with our findings suggests that heart rate is an important variable in predicting early HFNC outcomes in pediatric patients. To our knowledge, our study is the first study to evaluate the performance of the ROX-HR index in critically ill children $\leq$ 24 months old. Our study results suggest that the ROX-HR index performs well and may be a promising tool in the early identification of pediatric patients at risk for HFNC failure.

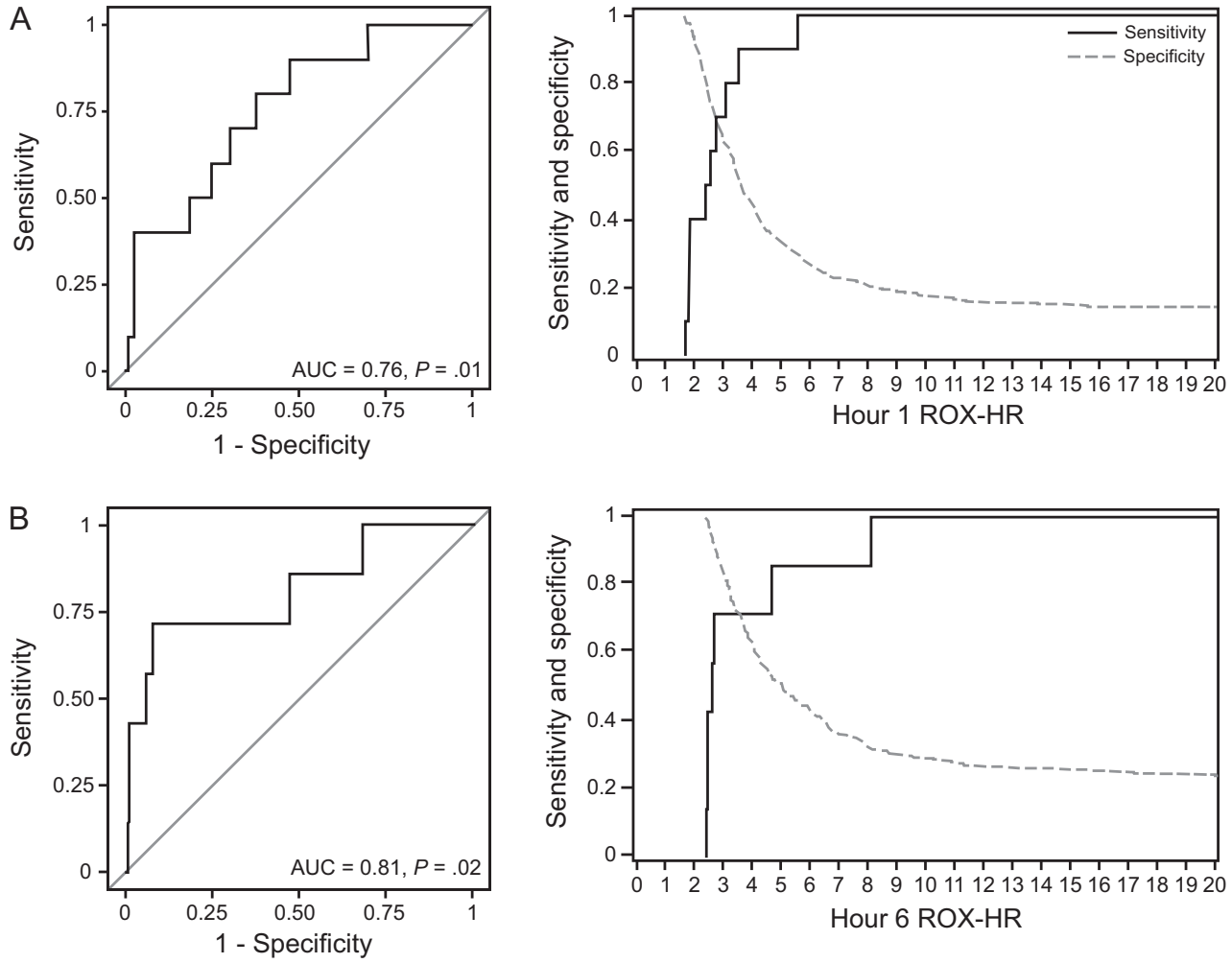

Fig. 3. Receiver operating characteristic curves for respiratory rate-oxygenation heart rate (ROX-HR) index at hour 1 (A) and hour 6 (B). AUC = area under the curve.

HFNC has been studied extensively in pediatric subjects younger than 24 months.[24] In our exploratory age-based analysis, we found that ROX-HR remained significant only in the subgroup of infants < 6 months of age. With nearly half of our cohort < 6 months old (49.1%), this finding indicates the greatest signal for ROX-HR was from the youngest subjects. Whereas the ROX-HR still may be useful in other age groups, our study may have been underpowered and, therefore, did not detect any difference. This is a limitation as well as a future direction of study.

There are several limitations of our study. First, this was a single-center, retrospective study. Documentation bias is possible, and external validity may also be impacted. Second, there is no standard definition regarding a flow that constitutes HFNC in pediatric patients. However, the median flows in both the success and failure cohorts are consistent with evidence-based HFNC use. Third, determining the best cutoff is a challenge. Provider preference and priorities may favor specificity versus sensitivity of a predictive model based on the clinical situation. In this study, sensitivity was favored as we wanted to identify the patients in need of early intervention and limit delays in care. This should help provide guidance to providers early into HFNC therapy and can be useful in a variety of clinical settings, specifically the emergency department, pediatric wards, as well as the PICU.

There are 2 important future directions. First, the ROX-HR index needs prospective validation. Second, race remained a significant predictor of HFNC failure in multivariate analysis. Currently, we are exploring how social determinants of health affect HFNC outcomes in this study population. In addition to strengthening a failure prediction model, this future analysis may inform community health interventions.

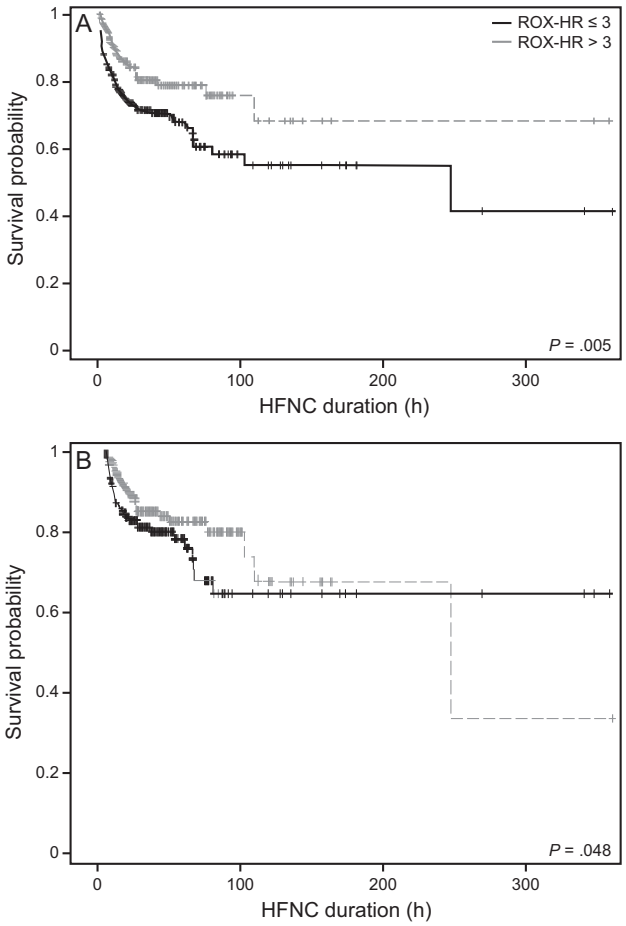

Fig. 4. Kaplan-Meier plots of high-flow nasal cannula (HFNC) success probability based on ROX-HR index at 1 h (A) and 6 h (B).

Conclusions

The ROX-HR appears to be a useful tool for early identification of HFNC failure in subjects ≤ 24 months old. A ROX-HR index < 3 at 1 and 6 h of HFNC use correlated with a high risk of HFNC failure and the need for escalation of care. Larger prospective studies are necessary to validate the role of the ROX-HR index in pediatric patients.

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