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RESEARCH

Association between respiratory rate oxygenation index and need for positive pressure ventilation in children on high flow nasal cannula for bronchiolitis

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Abstract

Our objective was to evaluate the association of respiratory rate oxygenation index (ROX) with the need for positive pressure ventilation in children < 2 years of age with bronchiolitis on high flow nasal cannula (HFNC) therapy. We performed a single-center prospective observational study of a convenience sample of children < 2 years of age with bronchiolitis who had HFNC initiated in the pediatric emergency department between November and March, 2018–2020. ROX was calculated as pulse oximetry/FiO_2/respiratory rate at HFNC initiation. Demographics, need for positive pressure ventilation (PPV), disposition, and hospital length of stay were collected. Logistic regression model was used to determine the odds ratio for PPV need relative to the highest ROX quartile. Of the 373 patients included, 49 (13.1%) required PPV. ROX was lower in patients who required PPV compared with those who did not (5.86 [4.71–7.42] vs. 6.74 [5.46–8.25]; $p = 0.01$). Logistic regression revealed that those patients whose ROX was in the lowest quartile (< 5.39) were three times more likely to require PPV compared to those in the highest quartile (> 8.21). These results held true after adjusting for confounders (odds ratio 3.1; 95% *CI* [1.3 to 7.5]; $p = 0.02$). The model's AUROC (0.701) indicated acceptable discrimination between cases and controls.

Conclusion: Low ROX index was associated with the need for PPV in children with bronchiolitis on HFNC. The risk stratification provided and ROX threshold for risk stratification require confirmation in other populations with a larger sample size.

What is Known:

- *Demographic and clinical factors associated with high flow nasal cannula (HFNC) therapy in children with bronchiolitis has been studied.*

What is New:

- *This is the first study to report the utility of association of Respiratory Rate Oxygenation (ROX) index for need for positive pressure ventilation (PPV) in children < 2 years of age with bronchiolitis on HFNC therapy.*
- *ROX was lower in children who required PPV and children whose ROX was in the lowest quartile (< 5.39) were three times more likely to require PPV compared to those in the highest quartile (> 8.21).*

Keywords High flow nasal cannula oxygen · Positive pressure ventilation · Bronchiolitis · Children

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Abbreviations

HFNC	High flow nasal cannula
PPV	Positive pressure ventilation
ROX	Respiratory rate oxygenation

Bronchiolitis is a leading cause of lower respiratory tract infection and hospitalization in infants [1]. While most children with bronchiolitis recover with supportive care, around 20% require intensive care unit (ICU) admission, 5% non-invasive ventilation, and 3% invasive mechanical ventilation [2]. Fujiogi et al. [3] evaluated bronchiolitis-related

hospitalization trends from 2000 to 2016 in the USA and found an increased proportion in overall hospitalizations from 16 to 18%. Furthermore, mechanical ventilation rates and hospital costs increased by 63% and 25% respectively.

High flow nasal cannula (HFNC) therapy is widely used as non-invasive respiratory support for bronchiolitis. Several studies sought to evaluate and identify demographic and clinical factors associated with HFNC failure [4–8]. However, despite considerable efforts, there remains lack of objective guidance to identify children with bronchiolitis at increased risk for requiring positive pressure ventilation (PPV).

Roca et al. [9, 10] devised and validated the respiratory rate oxygenation (ROX) index ratio: calculated as [pulse oximetry/FiO_2/respiratory rate]. The index was successfully used to predict need for mechanical ventilation in adults with pneumonia requiring HFNC therapy. Yildizdas et al. [11] attempted to translate the index's use to identify HFNC failure in children with varied etiologies of respiratory illness. The investigators established threshold ROX values to predict failure at 24 and 48 h after HFNC initiation. However, their sample size was small and only 13% had bronchiolitis. Moreover, their method incorporated respiratory rate z-scores. These elements limit generalizability and use as a bedside tool.

Our objective was to evaluate the association of respiratory rate oxygenation index (ROX) with the need for positive pressure ventilation in children ≤ 2 years of age with bronchiolitis on high flow nasal cannula (HFNC) therapy.

Methods

Design, setting, and inclusion criteria

We conducted a prospective observational study of children ≤ 2 years of age requiring HFNC support for bronchiolitis in the pediatric emergency department (PED). Our PED is a tertiary care, level-1 trauma center with > 85,000 annual visits, including approximately 600 admissions for bronchiolitis. Patients were enrolled during consecutive bronchiolitis seasons from November to March 2018–2020. Patient enrollment stopped March 1st 2020, because of restrictions on in-person enrollment secondary to the COVID-19 pandemic. We excluded children with bronchiolitis who (1) required low-flow oxygen or no respiratory support, (2) required immediate PPV secondary to presentation with apnea and bradycardia, (3) were directly admitted to the hospital, and (4) had non-English speaking caregivers or refused consent.

Our institution follows standardized PED and inpatient bronchiolitis pathways (supplemental file). These protocols detail indications for HFNC initiation, weaning, and criteria for ICU admission. According to this protocol, a respiratory severity assessment is performed on all children with bronchiolitis. This assessment includes work of breathing (none/mild, retractions, retractions with nasal flaring head bobbing), cough (infrequent, moderate/frequent, severe), breath sounds (clear, crackles/wheezing, crackles with wheezing, and poor air entry), and respiratory rate (age-based cutoffs). HFNC is initiated at 1 to 1.5 L/kg/min for those patients with severe disease or those with moderate disease who do not respond to low-flow oxygen. PPV is initiated for those children who present with apnea with bradycardia requiring intervention and is considered for those children who exhibit worsening of clinical status on respiratory support of HFNC > 2 L/kg/min or ≥ 50% FIO2 as assessed by work of breathing (respiratory rate above normal for age with severe chest wall retractions), perfusion status (prolonged central and peripheral capillary refill time > 3 s and hypotension for age), and altered sensorium/lethargy. This study was approved by our Institutional Review Board (011718MP4E).

We enrolled a convenience sample determined by research assistant availability (9.00 am to 9.00 pm on weekdays, and until 5.00 pm on weekends). Participants were identified from the presenting complaint on an electronic tracking board and orders for HFNC therapy initiation in the electronic medical record. Research assistants verified diagnosis and eligibility criteria and then obtained written informed consent from parents or guardians. All diagnostic studies and interventions were performed at the clinical team's discretion.

We collected patient demographics, history of prematurity, vital signs at presentation, ROX calculated at HFNC initiation, need and indication for ICU transfer, need for positive pressure ventilation (PPV), and hospital length of stay from the patient's electronic medical record.

Study definitions

Bronchiolitis was defined as symptomatic viral respiratory illness with rhinitis and cough, with or without signs of respiratory distress [1]. Patients were enrolled based on clinical diagnosis of bronchiolitis provided by PED physicians.

ROX index was calculated by the research assistant retrospectively based upon data obtained at the time of HFNC initiation as the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate.

Failure of HFNC therapy was defined as the need for PPV: continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or endotracheal intubation. Data on ICU transfers were collected; however, transfer alone, without need for PPV, was not considered an HFNC therapy failure.

Viral testing

At our institution, point-of-care testing for respiratory syncytial virus, influenza A and B virus, using polymerase chain reaction is performed in the PED on all children who require admission to the hospital with respiratory symptoms during the bronchiolitis season. An expanded respiratory viral panel polymerase chain reaction test was performed on select children based on the physician preference in the inpatient floor and ICU.

Statistical analysis

Proportions for demographic and clinical characteristics were compared using chi-square tests. Normally distributed continuous data were compared using *t*-tests and Wilcoxon rank-sum tests were used for non-normally distributed data. As a first step to examine potential association between ROX and PPV-need, we divided the calculated ROX values into quartiles. We constructed binary logistic regression models to determine odds ratios for PPV need expressed relative to the highest ROX quartile. Crude estimates were adjusted for potential confounding parameters: age, prematurity, incidence of apnea, race, and presence of positive viral test, based on construction of a directed acyclic graph. We assessed the model's goodness-of-fit using Hosmer–Lemeshow's χ [2] test. The model's ability to discriminate between patients who received PPV and those who did not was evaluated by AUROC calculation (area under the receiver operating characteristic curve). Stata (v15.1; StataCorp, College Station, TX) was used for analysis. Based on the assumption that 10% children with bronchiolitis would require PPV and results from Roca et al. [9], power analysis indicated a target sample size of 436.

Results

Figure 1 shows the enrollment flow-chart and Table 1 shows the demographic and clinical characteristics. Forty-nine children (13.1%) required PPV. The median duration on HFNC prior to PPV initiation was 8 h (IQR: 5–21) and the median duration on PPV was 2 days (IQR: 1–3). The

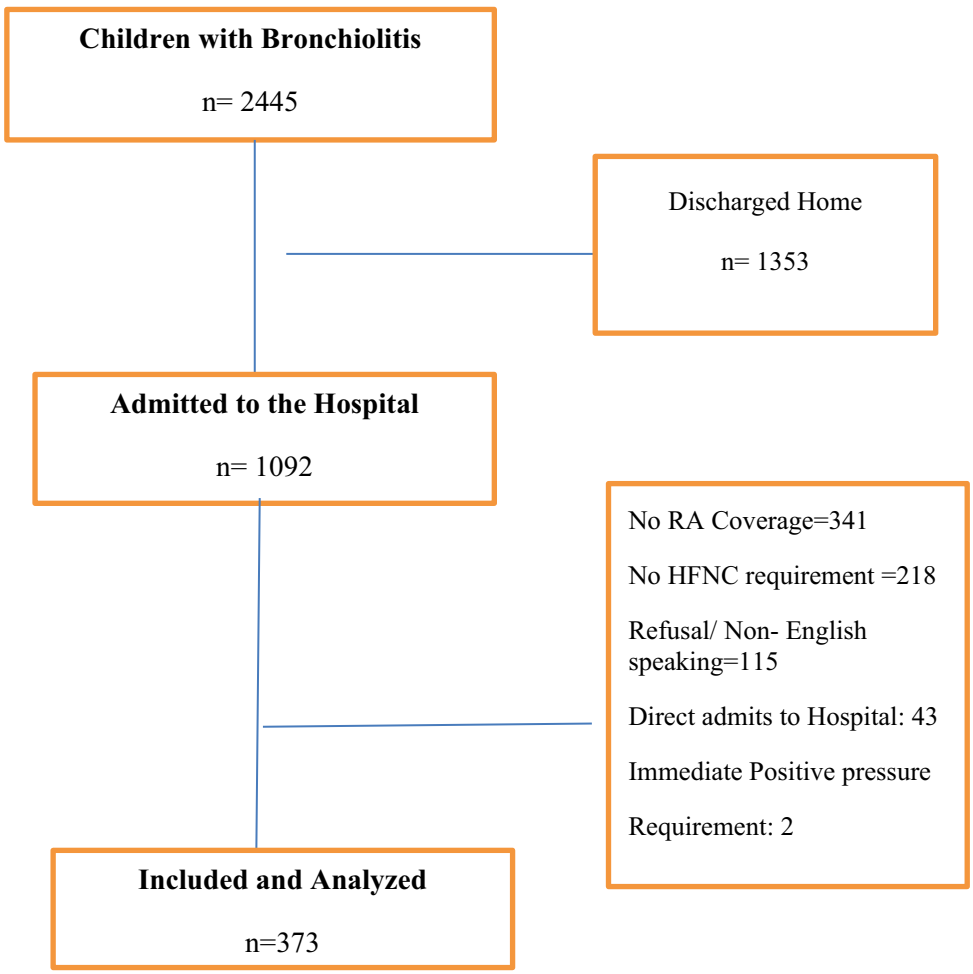

Fig. 1 Study flow sheet

Table 1 Demographic and clinical characteristics of the study cohort

	All ($n=373$)	PPV ($n=49$)	No PPV ($n=324$)	p-value
Male (%)	57 (52–62)	61 (47–74)	56 (51–61)	0.51
Premature (%)	23 (19–27)	22 (13–36)	23 (19–28)	0.95
Race (%)				**0.04**
African American	66 (62–71)	55 (41–68)	68 (63–73)	
Caucasian	25 (21–30)	37 (24–51)	24 (19–29)	
Other	2 (1–4)	2 (0–11)	2 (1–4)	
Unknown	6 (4–9)	6 (2–17)	6 (4–9)	
Age (days)	196 [90–334]	164 [83–291]	197 [94–347]	0.36
< 2 months (%)	15 (12–19)	14 (7–27)	15 (12–20)	0.84
Weight (Kg)	7.6 [5.5–9.7]	7.3 [5.5–9.0]	7.6 [5.5–9.7]	0.44
Fever (%)	21 (17–26)	27 (16–41)	20 (16–25)	0.33
Apnea (%)	3 (2–6)	4 (1–15)	3 (2–6)	0.71
Positive viral test (%)	61 (56–66)	82 (68–90)	58 (53–64)	**0.002**
Heart rate (beats per minute)*	156 (154–158)	159 (155–164)	155 (153–157)	0.13
Respiratory rate*	54 (52–55)	56 (52–60)	53 (52–55)	0.24
Oxygen saturation in room air (%)*	96.4 (96.0–96.8)	94.7 (93.1–96.3)	96.7 (96.3–97.0)	**0.02**
Hypoxia (%)	5 (3–8)	14 (7–27)	4 (2–6)	**0.002**
ROX	6.67 [5.39 to 8.21]	5.86 [4.71 to 7.42]	6.74 [5.46 to 8.25]	**0.01**
Hospital length-of-stay (hours)	57 [45 to 96]	142 [99 to 195]	52 [42, 76]	**0.0001**

Fever denotes initial temperature ≥ 38 °C; premature defined as < 37 weeks gestation; hypoxia defined as oxygen saturation of < 90% in room air

Missing data were as follows: race was unknown in 23 (3 in the PPV group), temperature was not recorded in one patient (no PPV), and initial oxygen saturation was not recorded in one patient (no PPV)

Proportions shown with 95% confidence intervals (*CI*). Continuous parameters show as either means followed by 95% *CI* in rounded brackets if data were normally distributed or as medians with IQR in square brackets if not normally distributed

*Values represent those measured on arrival to PED prior to initiation of HFNC

proportion of children with hypoxia was higher in those who received PPV, as was the proportion who tested positive for viral infection. There was an inter-group difference in race with proportionately fewer African American children who required PPV versus those who did not. Initial ROX was lower in patients who required PPV compared with those who did not (mean 5.9, 95% *CI* [4.7 to 7.4] versus 6.7 [5.5 to 8.3]; $p=0.01$). The median hospital length of stay was significantly longer in those who received PPV compared to those who did not receive PPV (142 [99 to 195] versus 52 [42, 76]; $p=0.001$).

The distribution of ROX values at HFNC initiation is shown in Fig. 2. The peak of the distribution, the bin centered at a ROX of 5.5, lies just above the cutoff of the lowest quartile (5.4).

The logistic regression model (Table 2) revealed that the odds ratio of PPV appeared constant over the upper three quartiles. However, children in the lowest ROX quartile (< 5.4) had three times higher odds for PPV compared with children in the highest quartile (> 8.2). This difference remained after adjusting for confounders (Table 2). The Hosmer–Lemeshow test p-value was 0.17, consistent with our model fitting the data. The model's AUROC was 0.701, an acceptable discriminator. [12]

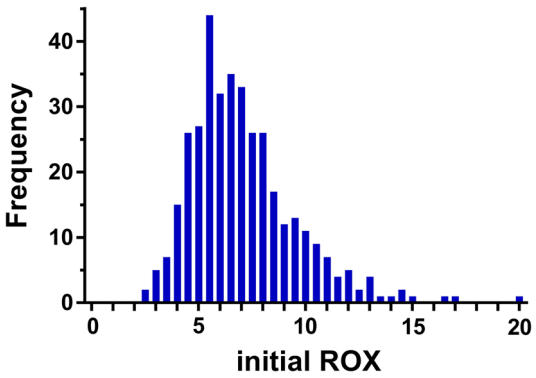

Fig. 2 Histogram of ROX at HFNC initiation

Discussion

We found an association between ROX index and PPV requirement in children with bronchiolitis on HFNC. Only patients in the lowest ROX quartile had higher odds ratio for HFNC failure and subsequent PPV. The latter observation suggests there may be a critical value of ROX below which the need for PPV is increased in children with bronchiolitis.

Table 2 Logistic regression model

	Crude model		Adjusted model	
ROX quartile	***OR* [95% *CIs*] * for PPV**	***p*-value**	***OR* [95% *CIs*] *for PPV**	***p*-value**
Second highest [8.21 ≥ ROX > 6.67]	1.48 [0.57 to 3.87]	0.42	1.32 [0.49 to 3.56]	0.58
Third highest [6.67 ≥ ROX > 5.39]	1.13 [0.41 to 3.05]	0.82	1.09 [0.39 to 3.00]	0.87
Lowest [ROX ≤ 5.39]	**3.10 [1.29 to 7.42]**	**0.01**	**3.06 [1.25 to 7.51]**	**0.02**

The model was adjusted for age (less than or more than 2 months), prematurity, incidence of apnea (yes/no), race, and presence of a positive viral test

*The odds ratios are expressed relative to the highest ROX quartile [ROX > 8.21]

ROX was first described by Roca et al. [9] in adult patients with severe pneumonia. A ROX index > 4.9, 12 h after HFNC initiation after adjustment for confounders, was associated with lower risk for mechanical ventilation. Their ROX threshold is close to the cutoff value in our lowest quartile (< 5.4), i.e., the one with the greatest odds ratio for need for PPV.

A meta-analysis [13] demonstrated ROX possessed good discrimination with a summary area under the curve of 0.81 (95% *CI*, 0.77–0.84), with sensitivity of 0.70 for HFNC-treated patients with COVID-19. The only ROX application in pediatrics used a relatively complex approach that involved ROX values and variation calculated at 24 and 48 h in 131 children who received HFNC for varied respiratory illnesses [11]. The authors used respiratory rate z-scores derived from a different population for ROX calculation. The final calculated index was successful in prediction of HNFC failure and therefore lends support to ROX's merit. Nonetheless, their study was limited because of small sample size (particularly those with bronchiolitis), lack of immediacy (48-h values were used), and relative complexity of calculation.

To our knowledge, this is the first study to evaluate potential association between ROX and PPV requirement in children with bronchiolitis. This association together with the finding that the odds ratio for PPV-need was increased only in the lowest ROX quartile raises the possibility of ROX as a screening tool to identify children with bronchiolitis likely to need PPV. The sensitivity and specificity obtained from the ROX quartiles are 43% and 76%, respectively, with an AUROC of 0.61 [95% *CI* 0.52 to 0.69]. These values are unsatisfactory for screening; however, our objective was to determine if an association existed between ROX and need for PPV, and we did not seek to optimize the ROX cutoff for screening. Further work with larger sample sizes is required to identify and establish appropriate ROX value cutoffs for screening.

Because respiratory interventions are required in a minority of patients with bronchiolitis, it is important to develop indicators to identify subsets of children with a higher likelihood of respiratory failure. Early identification of such children will aid timely intervention and resource allocation. While initial ROX assessment at presentation could serve as a tool to aid with optimal PED disposition, monitoring of serial scores may be helpful in children admitted to the inpatient settings for early identification of a subset of children who are likely to require escalation of care and respiratory support during hospitalization. Our study suggests children with ROX values ≤ 5.4 may benefit from close respiratory status monitoring. The risk for PPV was constant across the three upper ROX quartiles (range 9–12%). In contrast, the risk of PPV was doubled (23%) in the lowest ROX quartile.

There have been several clinical scoring systems [14–16] that have been developed to predict severity of bronchiolitis most of which include a combination of assessment of respiratory rate, wheezing, retractions nasal flaring, and oxygen saturation. However, only a few of them have been validated for use in the emergency department and none of them has emerged as an ideal score that can be used. Furthermore, the assessment of work of breathing especially the intensity of retractions can be subjective and can vary between observers. ROX does not include an assessment of work of breathing and uses objective parameters which may make it better to use at bedside. Mount et al. [17] recently derived and validated a Critical Bronchiolitis Score and established that this scoring performed better than PICU mortality-based scores in measuring expected duration of ICU-level respiratory support and length of stay in children admitted to the PICU for bronchiolitis. However, this scoring system includes 12 parameters all of which may not be readily available to clinicians and its use was limited to children with bronchiolitis admitted to the pediatric intensive care unit. Friere et al.[18] identified five parameters associated with escalated care in 2722 children with bronchiolitis, defined as hospitalization with HFNC requirement, need for invasive and non-invasive ventilation, and ICU admission. These parameters were oxygen saturation < 90% at presentation, nasal flaring or grunting or both, retractions, age ≤ 2 months, dehydration, and poor feeding. The strongest predictor was hypoxia (*OR* 8.9;

95% *CI* 5.1 to 15.7). ROX utilizes both oxygen saturation and fraction of inspired oxygen, consistent with hypoxia being a crucial determinant of care escalation.

Limitations

Our study was single-center and therefore generalizability may be limited. We enrolled a convenience sample. Nevertheless, when we examined data from missed eligible patients, we found no demographic or PPV rate differences. The study was halted before we reached target enrollment secondary to the COVID-19 pandemic. Therefore, the study may be underpowered to detect inter-quartile differences. We do not believe this occurred because there was no evidence for increased odds ratios until comparison with the lowest ROX quartile. However, effect size should be interpreted with caution because our small sample resulted in wide confidence intervals. In addition, the smaller-than-anticipated sample size impacted our ability to derive a screening tool. We assessed ROX at only one time, at HFNC initiation. Although serial measurements may refine association and prediction, assessment at first presentation would be the most useful in determination of PED disposition. We adjusted the regression model for age (a binary parameter: older and younger than two months of age). Nonetheless, there remains the possibility that differences in the normal range of respiratory rates across the study population contributed to our findings. Therefore, we examined age-distribution within each ROX quartile. We found no inter-quartile differences in median values or distribution, both for the entire cohort or if analysis was restricted to children who required PPV. These results suggest age-associated differences in respiratory rate did not influence the outcome. Finally, our results may not be applicable to institutions that follow a different protocol for HFNC initiation and treatment of bronchiolitis.

Conclusions

Low ROX index is associated with need for PPV in children with bronchiolitis on HFNC. Consequently, ROX index has potential to be used as a screening tool for risk stratification of children with bronchiolitis and appropriate PED disposition by early identification of those at risk for PPV. Our results should be confirmed in other populations with larger sample size, and an appropriate ROX threshold for increased risk for PPV in children with bronchiolitis defined.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-022-04607-4.

Authors' contributions Dr. NK conceptualized and designed the study, secured funding, provided supervisionand oversight for conduct of the study, drafted the intitial manuscript, and edited and revised the manuscript. Dr. PW performed the data curation and verification, conducted the statistical anlaysis, and edited and revised the manuscript. Dr. US designed the study, provided supervision and oversight for conduct of study, and edited and revised the manuscript. All authors have reviewed and approve the final manuscript as submitted.

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Availability of data and material N/A.

Code availability N/A.

Declarations

Ethics approval This study was approved by our Institutional Review Board (011718MP4E).

Consent to participate All parent provided written informed consent for participation in the study.

Consent for publication N/A

Competing interests The authors declare no competing interests.

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