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Original Article

Risk factors and outcomes of pediatric non-invasive respiratory support failure in Latin America

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ABSTRACT

Background: Noninvasive respiratory support (NRS) is standard in pediatric intensive care units (PICUs) for respiratory diseases, but its failure can lead to complications requiring invasive mechanical ventilation (IMV). This study aimed to identify risk factors for NRS failure in children with acute respiratory failure (ARF) in PICUs, and compare complications and outcomes between IMV-only and NRS failure patients.

Methods: We conducted a cohort study using data from the LARed Network prospective registry (April 2017–November 2022), in children under 18 years admitted to PICUs for ARF. Cases were divided into subgroups: those managed with IMV only, those who experienced NRS failure requiring IMV, those who received NRS successfully, and those who did not require NRS or IMV. Exclusions included patients with home respiratory support prior to

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admission, patients without PICU discharge at the cutoff date of the analysis and those with incomplete data. Multivariate mixed models analyzed NRS failure risk factors, and complications between the IMV-only and NRS failure groups, using centers as a random effect.

Results: A total of 7374 children met the inclusion criteria, with 6208 in the NRS group and 1166 in the IMV-only group. The NRS success rate was 85.3 %. Risk factors for NRS failure included age (median of 4.6 months, interquartile range of 2.1–14.2 months), history of prematurity (adjusted odds ratio [aOR]=1.53, 95 % confidence interval [CI]: 1.20 to 1.95) or malnutrition (aOR=1.85, 95 % CI: 1.18 to 2.91), suspected bacterial infection (aOR=5.12, 95 % CI: 4.05to 6.49), FiO_2 >30 % (aOR=1.52, 95 % CI: 1.18 to 1.97), severe hypoxemia with SpO_2/FiO_2 ≤150 (aOR=1.85, 95 % CI: 1.48 to 2.30), tachypnea (aOR=1.42, 95 % CI: 1.18 to 1.72), tachycardia (aOR=1.77, 95 % CI: 1.47 to 2.12), and lung consolidations (aOR=1.45, 95 % CI: 1.14 to 1.85) or interstitial infiltrates (aOR=1.29, 95 % CI: 1.05 to 1.58) on chest X-ray. There were no significant differences in morbidity, mortality, duration of IMV, or PICU length of stay between patients who received IMV only and those who experienced NRS failure. However, patients who experienced NRS failure were more likely to develop withdrawal symptoms related to sedative or opioid discontinuation and/or delirium (aOR=2.57, 95 % CI: 1.85 to 2.57).

Conclusion: This study identified key risk factors for predicting NRS failure in children with acute ARF in PICUs, including younger age, prematurity, malnutrition, suspected bacterial infection, FiO_2 >30 %, severe hypoxemia (SpO_2/FiO_2 ≤150), tachypnea, tachycardia, and radiological findings such as lung consolidation and interstitial infiltrates. Compared to patients managed with IMV from the start, those who experienced NRS failure were more likely to develop withdrawal symptoms and/or delirium, although clinical outcomes such as mortality, IMV duration, and PICU length of stay were similar in both groups.

Introduction

The use of noninvasive respiratory support (NRS) systems to treat acute respiratory failure (ARF) in children has increased significantly in recent years.[1,2] NRS is preferred to invasive mechanical ventilation (IMV) because it avoids the associated risks and complications associated with IMV.[3,4] It has become the standard of care for most respiratory conditions requiring admission to pediatric intensive care units (PICUs).[5,6]

NRS provides respiratory support without the risks of tracheal intubation and other complications associated with IMV.[7,8] NRS includes high-flow nasal cannulas (HFNC) and positive pressure systems such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), with many children using one or multiple systems interchangeably. Although most children in Latin America admitted to PICUs do not require IMV, we often fail to identify which patients are more likely to experience NRS failure, making it challenging to predict complications and understand the need for timely IMV.[9] Previous studies have described varied and sometimes contradictory risk factors for NRS failure.[10]

Additionally, it is also relevant to understand if outcomes differ between patients who receive NRS and then fail to IMV and those who were only exposed to IMV from the beginning, as some groups consider that using NRS may worsen lung damage, potentially leading to worse outcomes when NRS fails compared to using IMV directly.[11]

The aim of this study is two-fold. First, we seek to identify risk factors at admission that can be associated with NRS failure. Second, we aim to compare clinical outcomes between patients who failed NRS and those who were only treated with IMV.

Methods

Study design

The LARed ARF registry is a prospective international multicenter registry from Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Peru, Suriname, and Uruguay, with 45 centers uploading data.[12] The registry collects clinical data of children aged 0–18 years admitted to participating PICUs, whose main reason for admission is ARF, excluding neonatal perinatal diseases. Respiratory support systems, both invasive and noninvasive, as well as the protocols for their use and management, are at the discretion of each center and are not standardized for the registry. This provides a realistic perspective and incorporates an expected variability bias, which is controlled by using the centers as a random effect in the multivariate models.

Participants

For this analysis, we divided cases into four subgroups. Those who required NRS as initial support of any type or combination. These were then divided into those who did not require IMV (NRS success) and those who required IMV due to failure (NRS failure). The third group consisted of patients who directly received IMV without previous use of NRS (IMV only). The fourth group included cases that did not require NRS or IMV (No RS); these cases were only counted but not included in any comparisons. We excluded patients who had home respiratory support prior to admission, patients without PICU discharge at the cutoff date of the analysis, and those with incomplete data.

Risk factors for NRS failure

Potential risk factors were defined as those present at PICU admission: sex, age, weight, admission diagnosis, suspected viral or bacterial infection, respiratory comorbidities such as bronchopulmonary dysplasia, chronic lung damage (bronchiectasis, bronchiolitis obliterans, cystic fibrosis, among others), previous wheezing (asthma, recurrent wheezing, bronchial hyperreactivity, etc.), prematurity, malnutrition, heart, genetic, or neurological disease; admission fraction of inspired oxygen (FiO_2), pulse oximetry (SpO_2), respiratory rate (RR), heart rate (HR) and SpO_2/FiO_2 ratio, and the ROX index (SpO_2/FiO_2 divided by RR). Additionally, the Pediatric Index of Mortality (PIM3) and the Functional Status Scale (FSS) scores and the type of NRS used.[13,14] In selecting risk factors, we focused on those available within the registry and of known clinical relevance. The

registry was designed to minimize the burden on clinical staff, limiting the granularity of certain clinical parameters. Data were collected within the first hour of PICU admission as per PIM3 guidelines, capturing initial clinical status without major intervention adjustments. As a result, dynamic indices or changes over time during patient evolution were not included due to registry restrictions.

Outcomes of NRS failure vs. IMV only

For clinical outcomes at discharge, we considered all events after admission to the PICU such as mortality, residual morbidity (difference of three or more points in FSS score on admission *vs.* discharge), IMV duration, ventilator-free days, and PICU length of stay. All NRS and IMV complications were also collected: pneumonia, weaning failure, tracheostomy, withdrawal/deprivation/delirium symptoms related to sedative or opioid discontinuation, atelectasis requiring bronchoscopy, pneumothorax, airway injuries, or accidental extubation. Rescue therapies such as neuromuscular paralysis, prone ventilation, inhaled nitric oxide, and extracorporeal therapies were also identified.

Sample size

A formal sample size calculation was not performed as the LARed ARF registry provides many available cases. However, it was estimated that we had adequate statistical power and a significance level of 0.05, assuming prevalences of at least 5 % and odds ratios (OR) greater than 1.5.

Statistical analysis

After database cleansing, continuous variables were described with medians and interquartile ranges (IQRs) since they did not have a normal distribution, based on the Kolmogorov–Smirnov statistic. Categorical variables were presented by absolute and relative frequencies. The clinical trajectory of all respiratory support used was plotted using a Sankey diagram.

For the analysis of risk factors associated with NRS failure *vs.* NRS success, a bivariate analysis with simple logistic regression was performed. Data were described with crude OR and 95 % confidence intervals (95 % confidence interval [CI]). Variables that showed significant differences and clinical relevance were then included in a mixed multivariate logistic regression model to calculate adjusted odds ratios (aOR) with their 95 % CI using centers as a random effect to account for variability in clinical practices across sites. This approach enhances the robustness of our findings by controlling for differences in treatment protocols among participating centers, ensuring that the results reflect true patient-level associations. Collinearity and interactions were tested for each variable to obtain the final model.

For the comparison of clinical outcomes between the IMV alone group and the NRS failure group, similar steps were followed. A bivariate analysis with simple logistic regression was conducted to describe the crude OR and 95 % CI. Significant and clinically relevant variables were included in a mixed multivariate logistic regression model, with centers as a random effect, to calculate aOR with their 95 % CI. PICU length of stay for each group was presented using Kaplan–Meier survival curves, and the log-rank test was used to compare the survival distributions.

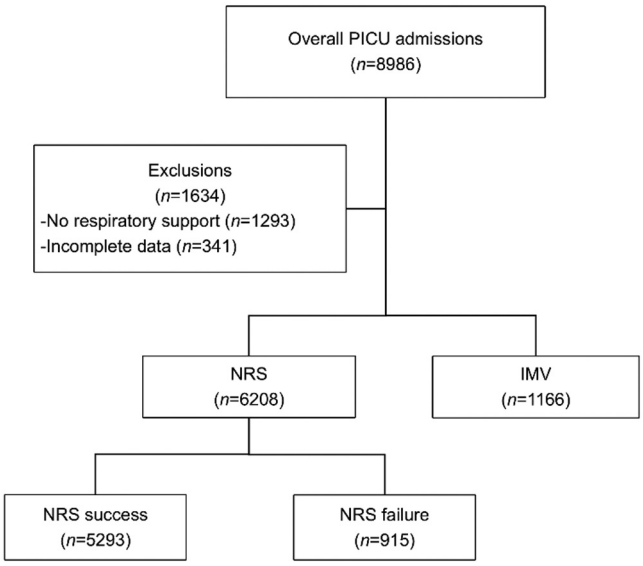

Figure 1. Flowchart of patients enrolled in the study.
IMV, Invasive ventilation; NRS, Non-invasive respiratory support; PICU, Pediatric intensive care unit.

The statistical software package STATA version 17 (StataCorp, 2021, Stata Statistical Software: Release 17, College Station, TX, USA: StataCorp LLC) was used for the analysis.

Ethics

This secondary analysis was presented and approved by the institutional review board (IRB) at Sociedad de Cirugía de Bogota Hospital de San Jose, FUCS (CEISH #IRB00011307, letter 0552-2021). Each center participating in the LARed registry has the approval of its respective IRB. For this analysis, a waiver of informed consent was approved since the analysis data is anonymized.

Results

General data

Between April 2017 and November 2022, a total of 8986 patients were enrolled in the ARF registry. Of these, 6208 patients received NRS and 1166 received only IMV, were included in the analysis (Figure 1). Across the 45 participating centers, the median number of patients treated with NRS was 34 (IQR: 4–205), with a median of 5 NRS failures per center (IQR: 1–28). The median number of patients treated solely with IMV was 12 per center (IQR: 5–27). Figure 2 details the trajectory of the different types of support used in the study after excluding those with incomplete data.

Risk factors associated with NRS failure

In our study, the rate of NRS failure was 14.7 %. Among the 6208 patients who received NRS, 3609 (58.1 %) were male, and the median age was 8.7 months (IQR: 3.0–26.4 months). Comparisons between patients who failed NRS and required intubation and those who had NRS success are given in Table 1.

Table 1
Comparison of patients with NRS success or failure.

Characteristics	NRS failure (*n*=915)	NRS success (*n*=5293)	OR	95 % CI	aOR	95 % CI
Sex*						
Female	366 (40.0)	2227 (42.1)	Ref.			
Male	549 (60.0)	3060 (57.8)	0.92	0.79 to 1.06		
Age*	4.6 (2.1–14.2)	9.7 (3.4–29.7)	**0.992**	**0.990** to **0.995**		
0–3 months	429 (47.1)	1523 (28.8)	Ref.		Ref.	
4–6 months	125 (13.7)	673 (12.7)	**0.66**	**0.53** to **0.82**	**0.56**	**0.43** to **0.73**
7–12 months	111 (12.2)	898 (17.0)	**0.44**	**0.35** to **0.55**	**0.34**	**0.26** to **0.44**
13–24 months	109 (12.0)	706 (13.3)	**0.55**	**0.44** to **0.69**	**0.41**	**0.31** to **0.55**
2–5 years	80 (8.8)	939 (17.7)	**0.30**	**0.24** to **0.39**	**0.24**	**0.17** to **0.34**
6–11 ears	34 (3.7)	455 (8.6)	**0.27**	**0.18** to **0.38**	**0.17**	**0.10** to **0.28**
12–18 ears	23 (2.5)	99 (1.9)	0.82	0.52 to 1.31	**0.52**	**0.29** to **0.93**
Weight (kg)*	6.4 (4.7–9.7)	8.6 (5.8–13.0)	1.000	1.000 to 1.000		
Admission diagnosis*						
Bronchiolitis	574 (62.8)	2682 (50.7)	Ref.			
Pneumonia	225 (24.6)	1133 (21.4)	0.93	0.78 to 1.10	0.83	0.63 to 1.09
Asthma/wheezing	49 (5.4)	1262 (23.9)	**0.18**	**0.13** to **0.24**	**0.44**	**0.30** to **0.65**
Other	66 (7.2)	213 (4.0)	**1.45**	**1.08** to **1.94**	**2.30**	**1.60** to **3.31**
Suspected infection†						
Viral	793 (86.7)	4777 (90.3)	**0.70**	**0.57** to **0.87**		
Bacterial	342 (37.4)	1266 (23.9)	**1.90**	**1.63** to **2.21**	**5.12**	**4.05** to **6.49**
Comorbidities*,†						
Bronchopulmonary dysplasia	70 (7.7)	241 (4.6)	**1.74**	**1.30** to **2.30**		
Chronic lung damage	26 (2.8)	83 (1.6)	**1.83**	**1.13** to **2.90**		
Wheezing	135 (14.8)	1690 (31.9)	**0.37**	**0.30** to **0.45**		
Prematurity	149 (16.3)	654 (12.4)	**1.34**	**1.13** to **1.69**	**1.53**	**1.2** to **1.95**
Heart disease	57 (6.2)	246 (4.7)	1.36	0.99 to 1.84		
Malnutrition	41 (4.5)	122 (2.3)	**1.99**	**1.35–2.88**	**1.85**	**1.18** to **2.91**
Genetic disease	39 (4.3)	158 (3.0)	1.45	0.98 to 2.01		
Neurological deficit	44 (4.8)	220 (4.2)	1.16	0.82 to 1.63		
Parameters						
Fraction of inspired oxygen* (FiO_2)	51 (32–78)	44 (30–60)	**1.01**	**1.009** to **1.015**		
FiO_2 >30 %	745 (83.2)	3950 (78.2)	**1.39**	**1.14** to **1.68**	**1.52**	**1.18** to **1.97**
O_2 saturation* (SpO_2)	96 (94–99)	97 (94–999)	**0.98**	**0.963** to **0.992**		
Hypoxemia (SpO_2 ≤88 %)	54 (5.9)	192 (3.6)	**1.66**	**1.21** to **2.29**		
Normoxemia (88< SpO_2 <97 %)	409 (44.8)	2419 (45.7)	Ref.			
Hyperoxemia (SpO_2 ≥97 %)	451 (49.3)	2678 (50.6)	1.00	0.86 to 1.15		
RR*,‡						
Bradypnea	15 (1.7)	41 (0.8)	**2.16**	**1.19** to **3.94**	**Ref.**	
RR normal	506 (55.5)	2991 (56.5)	Ref.			
Tachypnea	390 (42.8)	2261 (42.7)	1.02	0.88 to 1.18	**1.42**	**1** to **1.72**
HR*,‡						
Bradycardia	11 (1.2)	68 (1.3)	1.09	0.57 to 2.08	**Ref.**	
HR normal	543 (59.6)	3666 (69.3)	Ref.			
Tachycardia	357 (39.2)	1559 (29.5)	**1.55**	**1.34** to **1.79**	**1.77**	**1.47** to **2.12**
SpO_2/FiO_2*	192 (131–287)	233 (171–323)	**0.996**	**0.995** to **0.997**		
SpO_2/FiO_2 >250	269 (29.9)	2000 (39.1)	Ref.		**Ref.**	
150< SpO_2/FiO_2 ≤250	333 (37.0)	2256 (44.1)	1.10	0.92 to 1.30		
SpO_2/FiO_2 ≤150	298 (33.1)	860 (16.8)	**2.58**	**2.14** to **3.1**	**1.85**	**1.48** to **2.30**
ROX* index	3.92 (2.67–5.65)	4.93 (3.50–6.59)	**0.85**	**0.82** to **0.88**		
Radiological findings*						
Hyperinflation	298 (32.6)	2597 (49.1)	**0.50**	**0.43** to **0.58**		
Consolidation	234 (25.6)	1150 (21.7)	**1.24**	**1.05** to **1.46**	**1.45**	**1.14** to **1.85**
Interstitial infiltrate	605 (66.1)	3274 (61.9)	**1.20**	**1.04** to **1.40**	**1.29**	**1.05** to **1.58**
Admission score						
PIM3*	0.43 (0.22–0.88)	0.26 (0.16–0.79)	1.001	1.000 to 1.020		
FSS* baseline score	6 (6–7)	6 (6–7)	1.032	0.976 to 1.093		
NRS type*						
HFNC	546(59.7)	4311 (81.5)	**0.34**	**0.29** to **0.39**		
CPAP	101 (11.0)	409 (7.7)	**1.48**	**1.17** to **1.87**		
NIV (BiPAP or equivalent)	266 (29.1)	1389 (26)	1.15	0.98 to 1.35		

Data are presented as *n* (%) or median (interquartile range).
In bold are all statistically significant values. The reference category for each variable is indicated in the "OR" column. aORs are reported only for variables that demonstrated statistical independence in the multivariate model; nonsignificant results were removed for simplicity.

* Data missing: FiO_2, SpO_2/FiO_2, ROX index: 16 (1.7%) NRS failure and 178 (3.4%) NRS success; PIM3 scores 48 (5.2%) NRS failure and 385 (7.3%) NRS success. FSS scores 322 (35.2%) NRS failure and 1539 (29.1%) NRS success. Sex for 6 (0.1%), age for 4 (0.05%), weight for 10 (0.1%), admission diagnosis for 4 (0.05%), suspected infection for 4 (0.05%), comorbidities for 7 (0.08%), SpO_2 for 19 (0.3%), RR for 19 (0.3%), HR for 19 (0.3%), radiological findings for 6 (0.1%), NRS type for 4 (0.05%).

† Suspected infection and comorbidities were not mutually exclusive.

‡ Using percentile cutoffs based on age-specific reference tables for RR and HR.[30] Bradypnea is defined as an RR below the 5th percentile for a patient's age; tachypnea refers to an RR above the 95th percentile; normal RR is within the range between the 5th and 95th percentiles, adjusted for the patient's age. Bradycardia is defined as an HR below the 5th percentile for a patient's age; tachycardia refers to an HR above the 95th percentile; normal HR is within the range between the 5th and 95th percentiles, adjusted for the patient's age.

aOR, Adjusted odds ratio; BiPAP, Bilevel positive airway pressure; CI, Confidence interval; CPAP, Continuous positive airway pressure; FSS, Functional Status Scale; HFNC, High-flow nasal cannula; HR, Heart rate; NIV, Non-invasive ventilation; NRS, Non-invasive respiratory support; OR, Crude odds ratio; PIM3, Pediatric Index of Mortality version 3; RR, Respiratory rate.

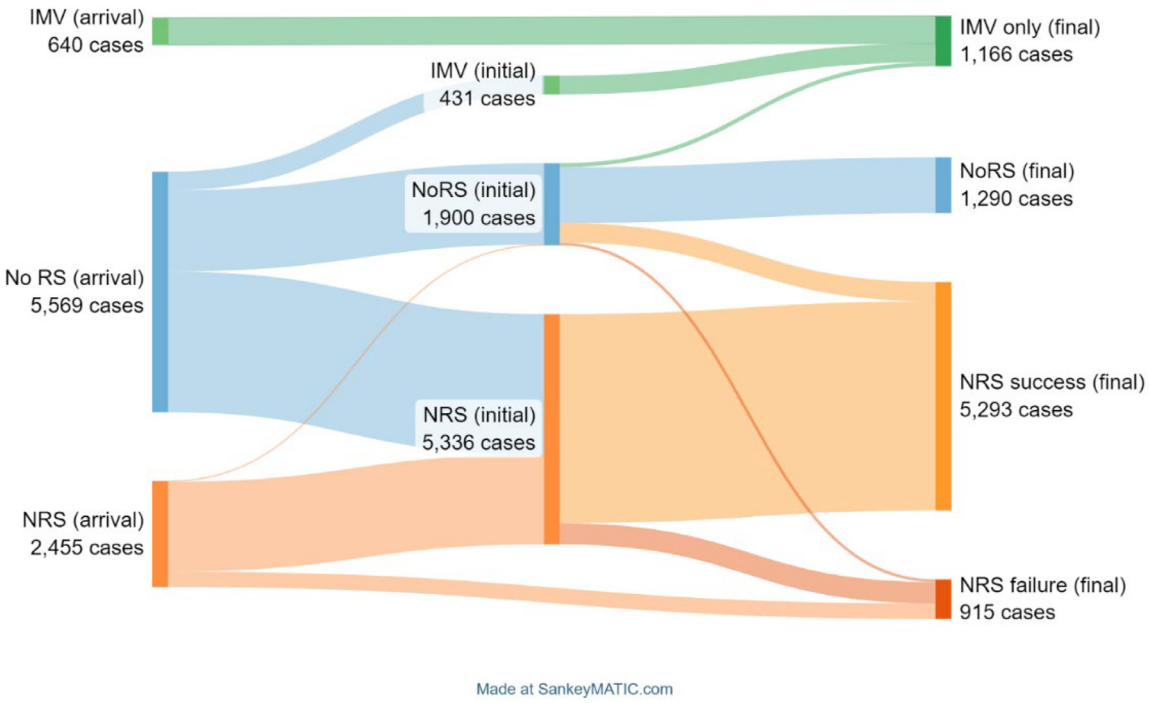

Figure 2. Patient trajectories and respiratory support interventions in the intensive care unit. This Sankey diagram illustrates the treatment pathways of 8664 patients admitted to the intensive care unit, showing the types and transitions of respiratory support provided at three critical stages. Upon arrival, the diagram indicates the type of respiratory support each patient received as they entered the ICU. The "Initial" stage represents the type of support determined to be necessary after the initial assessment in the unit. The "Final" stage shows the most intensive level of support utilized during the patient's stay. The widths of the flow paths reflect the proportions of patients transitioning between different support types, and absolute numbers at each node provide a clear count of patients in each category. The key identifies NRS, IMV, and cases where No RS was provided.
IMV, Invasive mechanical ventilation; No RS, No respiratory support; NRS, Non-invasive respiratory support.

The NRS failure group was significantly younger, with patients younger than 3 months presenting the highest failure risk.

Patients with asthma or wheezing had higher odds of success with NRS compared to those with bronchiolitis. Conversely, patients with suspected bacterial infections had a higher risk of NRS failure. Comorbidities such as prematurity and malnutrition were significantly associated with an increased risk of NRS failure.

Patients who required FiO_2 above 30 % had a higher risk of NRS failure. When evaluating the SpO_2/FiO_2 ratio, patients in the NRS failure group had lower median values, and specifically, patients with a SpO_2/FiO_2 ratio ≤150 demonstrated a significantly higher risk of NRS failure, with an aOR of 1.85 (95 % CI: 1.48 to 2.30).

Regarding the vital signs, patients with tachypnea (defined as a RR above the 95th percentile for age) had a higher risk of NRS failure; with an aOR of 1.42 (95 % CI: 1.18 to 1.72). Similarly, tachycardia (HR above 95th percentile for age) with an aOR of 1.77 (95 % CI: 1.47 to 2.12). Radiographic findings, including lung consolidation and interstitial infiltrates on chest X-rays, were also statistically associated with a higher risk of NRS failure. Evaluations of the PIM3 severity score and the baseline FSS score showed no statistically significant differences. Additionally, the use of HFNC was found to be a protective factor against NRS failure.

Outcomes of NRS failure vs. IMV only

Comparison of patients receiving IMV without prior NRS use only and those receiving IMV after NRS failure are given in Table 2. Significant withdrawal and/or delirium symptoms related to sedative or opioid discontinuation were found in patients who failed NRS. Additionally, these patients were at a higher risk of requiring rescue therapies compared to those who received IMV alone. However, there was no significant difference in mortality, duration of IMV, length of ICU stay, or new morbidity between patients who received IMV after NRS failure and those who were managed with IMV only.

A Kaplan–Meier graph in Figure 3 shows the differences in PICU length of stay according to the type of respiratory support used. Detailed information on admission factors for patients who received IMV and outcomes for successful NRS patients is available in the Supplementary Tables.

Discussion

In this international multicenter study, we identified several risk factors associated with NRS failure in children with ARF requiring PICU admission, including younger age, history of prematurity or malnutrition, suspected bacterial infection, initial use of elevated FiO_2, presence of tachypnea and/or tachycardia, and consolidation or interstitial infiltrates on chest X-ray. Conversely, wheezing and radiological findings of lung hyperinflation were associated with a lower risk of NRS failure. Additionally, our findings indicated that patients who failed NRS had higher rates of withdrawal, deprivation, or delirium symptoms related to sedative or opioid discontinuation, though no significant differences were observed in morbidity, duration of IMV, PICU stay, or mortality when compared to those who received IMV as their only respiratory support.

Table 2
Comparison of patients receiving IMV without prior NRS use or after NRS failure.

Characteristics	IMV only (*n*=1166)	NRS failure (*n*=915)	OR	95 % CI	aOR	95 % CI
Sepsis	370 (31.8)	220 (24.0)	**0.68**	**0.55** to **0.83**		
Septic shock	188 (16.1)	98 (10.7)	**0.62**	**0.48** to **0.82**		
Multiple organ failure	59 (5.1)	47 (5.1)	1.02	0.67 to 1.53		
ARDS*						
Any ARDS	377 (32.4)	286 (31.3)	0.95	0.78 to 1.15		
Mild	51 (4.4)	50 (5.5)	Ref.			
Moderate	143 (12.3)	105 (11.5)	0.76	0.48 to 1.21		
Severe	183 (15.7)	131 (14.3)	0.75	0.47 to 1.19		
Therapies received						
Antibiotics	1052 (90.2)	819 (89.5)	0.92	0.69 to 1.25		
Antivirals	97 (8.3)	70 (7.7)	0.91	0.65 to 1.27		
Antifungals	62 (5.3)	42 (4.6)	0.86	0.56 to 1.30		
Corticosteroids	438 (37.6)	340 (37.2)	0.98	0.82 to 1.18		
Blood products	338 (29.0)	275 (30.1)	1.05	0.87 to 1.28		
Any hospital infection	82 (7.1)	73 (8.0)	1.14	0.81 to 1.61		
IMV complications						
Any IMV complications	227 (19.5)	257 (28.1)	**1.62**	**1.32** to **1.98**		
Ventilator-associated pneumonia	53 (4.5)	27(2.9)	0.64	0.38 to 1.04		
IMV weaning failure	58 (5.0)	52 (5.7)	1.15	0.77 to 1.72		
Failure–tracheostomy	19 (1.6)	16 (1.8)	1.07	0.51 to 2.22		
Withdrawal/deprivation/delirium symptoms	92 (7.9)	176 (19.2)	**2.78**	**2.11** to **3.68**	**2.57**	**1.00** to **2.57**
Fiberoptic bronchoscopy atelectasis	5 (0.4)	9 (1.0)	2.31	0.69–8.79		
Pneumothorax on IMV	30 (2.6)	23 (2.5)	0.98	0.54 to 1.75		
Airway injury	25 (2.1)	26 (2.8)	1.3	0.74 to 2.43		
Accidental extubation	17 (1.5)	18 (2.0)	1.36	0.66 to 2.82		
Rescue therapies*						
Any rescue therapies*	389 (33.4)	365 (39.9)	**1.33**	**1.11** to **1.59**	**1.83**	**1.04** to **3.24**
Neuromuscular paralysis	354 (30.4)	328 (35.9)	**1.28**	**1.06** to **1.55**		
Prone position	133 (11.4)	123 (13.4)	1.21	0.92 to 1.58		
High-frequency ventilation	118 (10.1)	117 (12.8)	1.30	0.98 to 1.72		
Nitric oxide	20 (1.7)	22 (2.4)	1.41	0.73 to 2.74		
Surfactant	3 (0.3)	0	0.00	0.00 to 1.63		
ECMO	4 (0.3)	2 (0.2)	0.64	0.06 to 4.45		
Discharge FSS score*	7 (7–8)	7 (7–7)	**0.88**	**0.85** to **0.93**		
FSS score difference (diff)*	1 (0–1)	1 (0–1)	0.97	0.91 to 1.04		
New morbidity* (FSS diff >2)	58 (5.0)	45 (4.9)	0.82	0.53 to 1.27		
IMV duration* (h)	135 (79–209)	123 (64–219)	1.000	1.000 to 1.000		
ICU length of stay* (days)	8.6 (5.3–12.9)	10.2 (7.3–14.8)	*1.000*	0.997 to 1.008		
Dead	83 (7.1)	51 (5.6)	0.77	0.54 to 1.10		
Ventilator-free days*	22 (18–25)	22 (18–24)	1.33	0.98 to 1.82		

Data are presented as *n* (%) or median (interquartile range).

* Data missing: ARDS severity data 29 (2.5%) IMV-only, and 19 (2.1%) NRS failure; hospital infections 13 (1.1%) IMV-only patients, and 8 (0.9%) NRS failure. Rescue therapies 11 (0.9%) IMV-only, and 8 (0.9%) NRS failure; FSS score at discharge 37 (3.2%) IMV-only, and 23 (2.5%) NRS failure; new morbidity 12 (1.0%) IMV-only patients, and 6 (0.7%) NRS failure patients. IMV hours data 7 (0.6%) IMV-only, and 4 (0.4%) NRS failure; ICU length of stay 10 (0.9%) IMV-only, and 6 (0.6%) NRS failure; ventilator-free days 19 (1.6%) IMV-only patients, and 10 (1.1%) NRS failure patients.

aOR, Adjusted odds ratio; ARDS, Acute respiratory distress syndrome; CI, Confidence interval; ECMO, Extracorporeal membrane oxygenation; FSS, Functional Status Scale; ICU, Intensive care unit; IMV, Invasive mechanical ventilation; NRS, Non-invasive respiratory support; OR: Crude odds ratio.

In bold are all statistically significant values. The reference category for each variable is indicated in the "OR" column. aORs are reported only for variables that demonstrated statistical independence in the multivariate model; non-significant results were removed for simplicity.

Risk factors associated with NRS failure

Our study's high overall success rate of NRS is consistent with other contemporary studies, where the reported rate varies between 80 % and 90 %.[15,16] We also identified risk factors, such as age under 3 months old, that are consistent with similar studies.[17,18]

Furthermore, the need to use FiO_2 above 0.3 was associated with a higher risk of NRS failure. Additionally, patients with severe SpO_2/FiO_2 ratio (≤150) had a significantly higher risk of NRS failure, which was previously described.[19] Radiological findings of consolidation and interstitial infiltrate were also associated with a higher risk of NRS failure, like previous studies.[20]

In terms of the type of NRS used, we found the use of HFNC as a protective factor for failure; however, this result may be biased since the patients probably failed after therapeutic escalation to CPAP or BiPAP before IMV. Results reported in studies are variable, in 2020, Habra et al.[21] published results of a retrospective study of children with acute bronchiolitis in the PICU and found a higher rate of HFNC failure compared to BiPAP or CPAP. Zhong et al.[22] in 2022 published a meta-analysis including 541 children <24 months of age from five randomized controlled clinical trials (RCT), in which the treatment failure rate was significantly higher in the HFNC treatment group when compared with CPAP and BiPAP. In Borgi et al.[23] RCT in 2021, it was documented that treatment success was significantly higher in CPAP/BiPAP group compared to the HFNC group. Our study found that patients with asthmatic/wheezing attacks showed a high success rate with NRS, aligning with literature that highlights their distinct pathophysiological response to respiratory support. In contrast, for bronchiolitis,

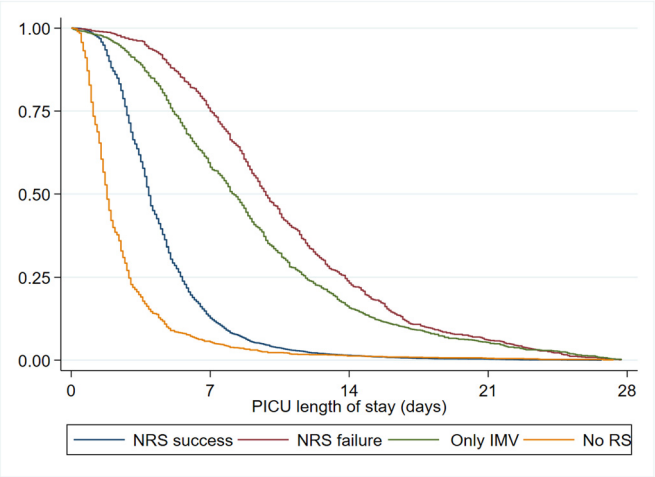

Figure 3. Kaplan–Meier graph with distribution of PICU length of stay (days) according to the four study groups. This graph illustrates the PICU length of stay distributed among four different groups: NRS success, NRS failure, IMV only, and No RS. The log-rank test revealed significant differences in length of stay between these groups ($\chi^2(3)=309.4$, $P<0.0001$).
IMV, Invasive mechanical ventilation; No RS, No respiratory support; NRS, Non-invasive respiratory support; PICU, Pediatric intensive care unit.

meta-analyses have reported that in moderate/severe cases, NRS with CPAP demonstrated a lower risk of therapeutic failure and a longer time until failure.[24] Some studies report a higher rate of HFNC failure compared to BiPAP or CPAP,[21–23] while others found a lower risk of therapeutic failure and a longer time until failure with NRS with CPAP in moderate/severe cases of bronchiolitis.[24]

Outcomes of NRS failure vs. IMV only

Our study found that patients with NRS failure had a higher risk of presenting withdrawal, deprivation, or delirium, potentially related to the use of sedatives during NRS to allow better adaptation.[25] We did not find statistically significant differences between patients who required IMV alone and those who failed NRS in terms of morbidity, hours of IMV, ventilator-free days, length of PICU stay, or mortality. In contrast, Kyle et al.[26] found significant differences in ICU-free days between non-invasive ventilation success ([22.9±6.9] days), non-invasive ventilation failure ([13.0±6.6] days), and mechanical ventilation ([12.5±6.9] days) groups, but no differences in ventilator-free days. Kopp et al. [27] reported similar data, with additional higher 28-day (5 % *vs.* 4 %) and 90-day (8 % *vs.* 5 %) in hospital mortalities. A meta-analysis by Boghi et al.[28] found that CPAP and BiPAP were associated with a lower rate of intubation compared to HFNC and standard low-flow oxygen (RR=0.78; 95 % CI: 0.62 to 0.98, $P = 0.03$), with a trend toward shorter PICU stay. Recently, Pelletier et al.[29] highlighted a significant increase in the use of NRS methods like HFNC in PICUs, reporting that HFNC use rose from 1.4 % in 2010 to 52.8 % in 2020, without a corresponding decrease in intubation rates or mortality. This suggests a potential overuse of non-invasive methods that may not translate to improved outcomes. Our study reflects these real-world practices, indicating that while HFNC is widely used, it may not always offer superior outcomes compared to positive pressure systems like CPAP or BiPAP. This highlights the gap between controlled study environments and everyday clinical practice, where subjective factors and the absence of rigid protocols may influence outcomes.

Strengths and limitations

Our study has strengths, such as being among the first multicenter study conducted in Latin America with enough patients for robust multivariate analysis to our knowledge. Moreover, our work reflects a clinical scenario not controlled by the investigator, which may be more representative of daily clinical practice. However, several limitations and potential sources of bias were identified. The lack of standardized protocols for ventilation management and intubation criteria across participating centers introduces variability that may affect the generalizability of our findings. This variability was controlled by using centers as a random effect in the multivariate models. Information bias could occur due to variations between centers and countries, which we minimized by collecting prospective data using standardized forms and definitions for data collection and cross-validation. The registry used was designed to minimize clinician burden, which limits the availability of detailed clinical parameters like dynamic indices and organ failure metrics. The data were collected manually, primarily within the initial admission window (first hour), so we lack dynamic and early evolution data, which have been described in other studies. Additionally, other confounding factors were controlled by including variables in the multivariate models, such as age, sex, comorbidities, and severity of illness at admission. These limitations underscore the importance of collaborative networks, which aim to reduce inconsistencies over time as protocols become more standardized through shared practices and strong evidence. In pediatrics, where decisions regarding intubation are particularly challenging due to limited consensus, such collaborations are crucial. Future research should focus on developing standardized protocols to improve consistency and patient outcomes. The study is also limited to non-invasive to invasive failure and did not account for failure within NRS systems. Furthermore, the study's findings may not be transferred to other clinical contexts, and they must be corroborated in prospective studies with a different design.

Conclusions

This study has identified risk factors that may help predict the failure of NRS in children with ARF admitted to the PICU. Factors such as younger age, history of prematurity or malnutrition, suspected bacterial infection, initial use of elevated FiO_2, presence of tachypnea and/or tachycardia, and consolidation or interstitial infiltrates on chest X-ray were significantly associated with NRS failure. Conversely, wheezing and radiological findings of lung hyperinflation were associated with a lower risk of NRS failure.

Additionally, NRS failure can result in iatrogenic withdrawal, but children who require IMV have comparable clinical outcomes to those exposed only to IMV. These findings suggest that a trial of NRS, especially in children with a low risk of failure, is likely to be a good strategy for achieving the best outcomes.

Collaborators

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Ethics Statement

All centers have received IRB approval, except for the waiver of informed consent for the registry. This secondary analysis was submitted to and approved by the lead IRB in Sociedad de Cirugia de Bogota Hospital de San Jose.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT to rectify translation and enhance the overall readability of the manuscript. After utilizing this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.09.001.

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