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Early Clinical and Physiological Predictors of High-Flow Nasal Cannula Failure in Infants With Acute Bronchiolitis: A Systematic Review

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Abstract

Acute bronchiolitis is a common cause of respiratory distress in infants, and high-flow nasal cannula (HFNC) therapy is frequently used to provide noninvasive respiratory support. However, treatment failure requiring escalation of respiratory support remains an important clinical concern. This systematic review aimed to identify clinical and physiological predictors of HFNC failure in infants and young children with acute bronchiolitis.

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, and supplementary sources were searched through October 1, 2026. Eligible observational studies and relevant secondary analyses of clinical trials were included. Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool. Findings were synthesized narratively because differences in study characteristics, predictor assessment time points, statistical methods, and definitions of HFNC treatment failure precluded clinically meaningful quantitative pooling.

A total of 1,358 records were identified, including 1,286 from electronic databases and 72 from supplementary sources. Thirteen studies met the inclusion criteria. Younger age, lower body weight, increased respiratory rate, tachycardia, hypercapnia, greater clinical severity, and persistent oxygen requirements were associated with HFNC failure, although findings varied across studies. The respiratory rate-oxygenation (ROX) index demonstrated limited discriminatory performance at baseline and one hour after HFNC initiation, with area under the receiver operating characteristic curve (AUC) values of 0.56 at both time points. At 12 hours after HFNC initiation, the ROX index demonstrated moderate discriminatory performance in predicting treatment failure, although differences in outcome definitions and study methodologies limited direct comparability.

Younger age, lower body weight, greater clinical severity, hypercapnia, persistent respiratory distress, and increased oxygen requirements may help identify infants at risk of HFNC treatment failure. Serial clinical and physiological assessment may provide more useful prognostic information than isolated baseline measurements. Although the ROX index demonstrated moderate discrimination at 12 hours in two studies, differences in treatment failure definitions and study methodologies limit direct comparability and the establishment of universal prediction thresholds. The ROX index should not be used as the sole criterion for treatment escalation. Further prospective multicenter studies using standardized failure definitions and consistent assessment intervals are needed to improve clinical prediction and decision-making.

Categories: Emergency Medicine, Pediatrics, Pulmonology
Keywords: acute bronchiolitis, clinical predictors, high-flow nasal cannula (hfnc), physiological predictors, rox index, systematic review, treatment failure

Introduction And Background

Acute bronchiolitis is a frequent respiratory illness during infancy, particularly in children younger than one year. Inflammation and mucus accumulation within the small airways can lead to increased breathing effort and impaired oxygenation. Affected infants commonly present with rapid breathing, wheezing, chest retractions, and feeding difficulties. While most children recover with supportive care, those with more severe respiratory involvement may require hospitalization and additional respiratory assistance [1].

High-flow nasal cannula (HFNC) therapy is commonly used to support infants experiencing moderate-to-severe respiratory difficulties due to bronchiolitis. By providing warmed, humidified gas at increased flow rates, HFNC can improve oxygen delivery and help reduce the effort required for breathing. Nevertheless, some infants do not respond adequately and require more intensive respiratory support, such as continuous positive airway pressure (CPAP), other noninvasive ventilation methods, or mechanical ventilation. Recognizing an inadequate response early is important to avoid delays in escalating respiratory care [2].

Previous investigations have examined a range of clinical and physiological indicators to identify infants who may not respond successfully to HFNC therapy. These include patient age, respiratory and heart rates, oxygen saturation, respiratory severity scores, and the respiratory rate-oxygenation (ROX) index. The ROX index is a composite physiological measure calculated by dividing the ratio of peripheral oxygen saturation (SpO_2) to the fraction of inspired oxygen (FiO_2) by the respiratory rate (RR): $ROX = \frac{\mathrm{SpO_2}/\mathrm{FiO_2}}{\mathrm{RR}}$. SpO_2 is expressed as a percentage, FiO_2 as a decimal fraction, and RR as breaths per minute. This index combines oxygenation status and respiratory rate and has been investigated as a potential predictor of HFNC treatment outcomes [3,4]. However, the usefulness of these indicators has differed across studies. Milesi et al. [3] found that early ROX measurements had limited ability to distinguish between treatment success and failure, whereas Nascimento et al. [4] reported better discriminatory performance when the index was assessed 12 hours after HFNC initiation. These findings indicate that both the selection of predictors and the timing of their measurement require further evaluation.

The differences observed across previous studies highlight the need to examine which clinical and physiological measures are most useful for identifying infants at risk of HFNC treatment failure. This systematic review therefore evaluates the reported predictors, their associations with treatment outcomes, and their predictive performance at different assessment times. Given the variability in study methodologies and definitions of treatment failure, the available evidence is synthesized narratively to preserve clinical interpretability. The aim is to provide evidence that may help clinicians recognize inadequate treatment responses and make timely decisions about respiratory support escalation.

Review

Materials and methods

This systematic review examined clinical and physiological predictors of HFNC failure in infants and young children with acute bronchiolitis. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [5] and was registered in PROSPERO (CRD420261536931). Findings were synthesized narratively due to variations in study methodologies and definitions of HFNC treatment failure.

Search Strategy

A comprehensive literature search was conducted across five electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library, to identify studies investigating clinical and physiological predictors of HFNC treatment failure in infants and young children with acute bronchiolitis. The search strategy combined three principal concepts: (1) acute bronchiolitis, (2) HFNC or high-flow oxygen therapy, and (3) treatment failure or potential clinical and physiological predictors. Medical Subject Headings (MeSH), Emtree terms, and free-text keywords were incorporated as appropriate for each database, using Boolean operators (AND and OR), truncation, and database-specific field tags. Search terms included “bronchiolitis,” “high-flow nasal cannula,” “HFNC,” “high-flow oxygen therapy,” “treatment failure,” “predictors,” “risk factors,” “respiratory rate,” “heart rate,” “oxygen saturation,” “hypercapnia,” and “ROX index.”

No restrictions were applied regarding publication year or language. The final search date was October 1, 2026. Electronic database searching was supplemented by Google Scholar searches, manual screening of reference lists from relevant primary studies and reviews, and forward citation tracking to identify additional eligible reports. According to the study identification records, 1,286 records were identified through electronic databases and 72 additional records through supplementary sources. The complete database-specific search strategies, including search expressions, execution details, and records retrieved, are presented in the Appendices (Supplementary Material 1). Supplementary search methods and corresponding records are reported in Supplementary Material 2, while the study selection and screening process is summarized in Supplementary Material 3.

Eligibility Criteria

Studies were eligible for inclusion if they enrolled infants and young children younger than 24 months diagnosed with acute bronchiolitis who received HFNC therapy. Eligible study designs included prospective and retrospective cohort studies, case-control studies, observational studies, and relevant secondary analyses of randomized controlled trials, provided that they investigated at least one clinical or

physiological factor associated with HFNC treatment failure. Relevant predictors included demographic characteristics, respiratory rate, heart rate, oxygen saturation, blood gas parameters, clinical severity scores, oxygen requirements, and composite physiological indices such as the ROX index. HFNC treatment failure was defined according to the criteria reported by each individual study, generally involving escalation to CPAP, other forms of noninvasive ventilation, or invasive mechanical ventilation. Differences in failure definitions across studies were documented and considered during evidence synthesis.

Studies were excluded if they primarily investigated respiratory conditions other than acute bronchiolitis, included children aged 24 months or older without separately extractable data for the eligible age group, or did not report relevant clinical or physiological predictors in relation to HFNC treatment outcomes. Case reports, narrative reviews, editorials, and studies lacking sufficient information to evaluate HFNC treatment failure were excluded. Where potentially overlapping participant populations were identified, study characteristics, recruitment settings, and enrollment periods were compared to minimize duplicate inclusion. Studies reporting distinct, nonoverlapping cohorts were considered independently.

Study Selection and Data Extraction

All records identified through electronic databases and supplementary sources were compiled, and duplicate records were removed before screening. Titles and abstracts were screened against the predefined eligibility criteria, followed by full-text assessment of potentially eligible studies. Two reviewers independently evaluated study eligibility at both screening stages, and disagreements were resolved through discussion and consensus, with consultation of a third reviewer when necessary. Reasons for full-text exclusion were documented, and the study selection process was summarized using a PRISMA 2020 flow diagram.

Data extraction was performed independently by two reviewers using a standardized data extraction form. Extracted information included the first author, publication year, country, study design, sample size, participant characteristics, HFNC treatment protocols, definitions of treatment failure, clinical and physiological predictors, and the timing of predictor assessment. Where available, effect estimates, including odds ratios, risk ratios, hazard ratios, and corresponding 95% confidence intervals, were extracted. Measures of predictive performance, including the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and reported cutoff values, were also recorded. Discrepancies were resolved through consensus or consultation with a third reviewer. Potentially overlapping study populations were assessed to prevent duplicate inclusion in the evidence synthesis.

Risk-of-Bias Assessment

The methodological quality of the included prognostic factor studies was assessed using the Quality in Prognosis Studies (QUIPS) tool [6]. Six domains were evaluated: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain was classified as having a low, moderate, or high risk of bias according to the methodological information reported in the included studies.

Two reviewers independently assessed each study, and disagreements were resolved through discussion and consensus, with consultation of a third reviewer when necessary. Particular attention was given to participant selection, completeness of follow-up, consistency of prognostic factor measurements, definitions of HFNC treatment failure, adjustment for potential confounders, and appropriateness of statistical analyses. Study-level judgments were summarized in the "Risk-of-Bias Assessment Using the QUIPS Tool" table, and potential sources of bias were considered when interpreting the findings of the narrative synthesis.

Statistical Analysis

A narrative synthesis was conducted to summarize the clinical and physiological predictors of HFNC treatment failure. Quantitative pooling was not performed because of differences in study populations, predictor definitions, assessment time points, statistical adjustment methods, and treatment failure criteria. Reported effect estimates, including odds ratios, hazard ratios, and their corresponding 95% confidence intervals, were summarized descriptively [7].

The predictive performance of the ROX index at 12 hours was evaluated using findings from two studies involving 228 participants. However, their definitions of HFNC failure differed, with one including escalation to noninvasive or invasive ventilation and the other considering invasive mechanical ventilation alone. Therefore, study-specific AUC estimates and failure proportions were presented separately without quantitative pooling to preserve clinical interpretability.

Results

Study Selection

The literature search identified 1,358 records, comprising 1,286 records from five electronic databases and 72 from additional sources, including Google Scholar (n = 46), reference list screening (n = 20), and forward citation tracking (n = 6). After removing 321 duplicates from the database records, 965 records underwent title and abstract screening, of which 884 were excluded. The remaining 81 database reports were retrieved and assessed for eligibility, with 73 excluded. Separately, all 72 reports identified through additional sources were assessed for eligibility, and 67 were excluded. Overall, 153 reports underwent eligibility assessment, of which 140 were excluded. Consequently, 13 studies were included in the systematic review and synthesized narratively. The study selection process is illustrated in the PRISMA 2020 flow diagram (Figure *1*).

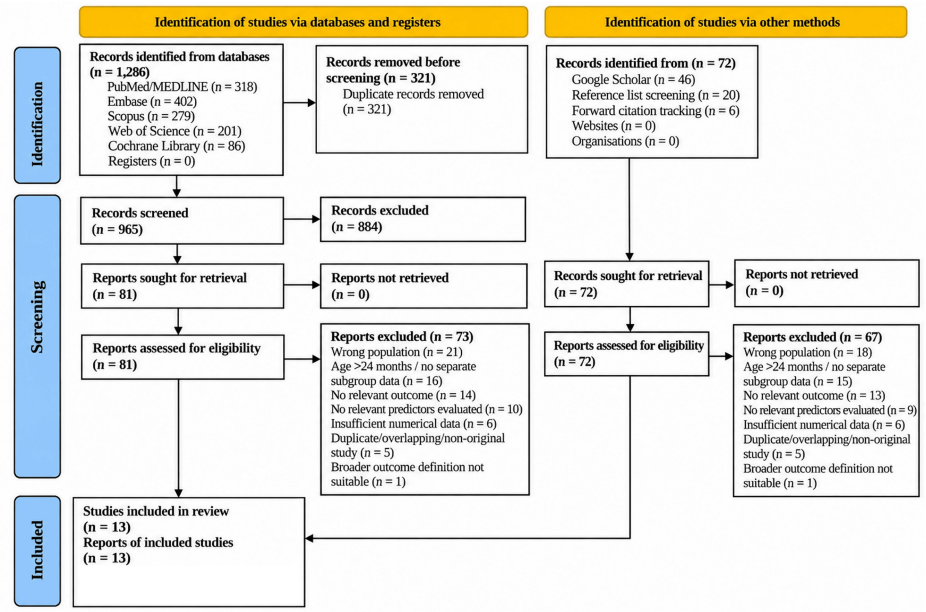


FIGURE 1: PRISMA 2020 flow diagram

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Characteristics of the Included Studies

The working evidence set comprised 13 independent study cohorts published between 2012 and 2025. These studies investigated clinical and physiological predictors of HFNC treatment failure in infants and young children with acute bronchiolitis. The main predictors included respiratory rate, heart rate, blood gas parameters, clinical severity scores, oxygenation indices, and the ROX index. Study characteristics are presented in Table *1*.

Author, Year	Country	Study Design	Sample Size (n)	Main Predictors	Clinical Setting	Definition of HFNC Failure
Abboud et al., 2012 [8]	USA	Retrospective cohort	113	Respiratory rate, pCO_2, weight	PICU	Requirement for endotracheal intubation
Guillot et al., 2018 [9]	France	Observational study	55	pCO_2, heart rate, pH	PICU	Escalation from HFNC to CPAP or BiPAP
Kamit et al., 2020 [10]	Türkiye	Retrospective study	84	Tachycardia, dehydration, pH	Pediatric emergency department	Escalation to noninvasive or invasive mechanical ventilation
Nascimento et al., 2021 [11]	Brazil	Retrospective observational	83	Respiratory rate, SpO_2	PICU	Requirement for noninvasive or invasive mechanical ventilation
D'Alessandro et al., 2021 [12]	Canada	Retrospective cohort	208	Age, Modified Tal score	Tertiary-care PICU	Escalation to noninvasive positive-pressure ventilation or invasive mechanical ventilation
Baquedano-Lobera et al., 2022 [13]	Spain	Retrospective observational	149	Hypercapnia, severity score	PICU	Escalation from HFNC to noninvasive ventilation (CPAP/BiPAP) or invasive mechanical ventilation due to inadequate clinical response or worsening respiratory distress
Kannikeswaran et al., 2022 [14]	USA	Prospective observational	373	ROX index	Pediatric emergency department	Requirement for positive-pressure ventilation
Milesi et al., 2024 [3]	France	Secondary trial analysis	286	ROX, ROX-HR, mWCAS	Multicenter pediatric critical care setting	Prespecified clinical deterioration criteria, including worsening respiratory distress, increased respiratory rate, discomfort, or severe apnea
Nascimento et al., 2024 [4]	Brazil	Prospective multicenter	102	ROX index, oxygenation	Two PICUs	Escalation from HFNC to noninvasive or invasive mechanical ventilation
Etrusco Zaroni Santos et al., 2024 [15]	Brazil	Secondary trial analysis	126	ROX, WDF, SpO_2/FiO_2	Tertiary pediatric hospital; emergency department/PICU	Requirement for invasive mechanical ventilation
Westphal et al., 2025 [16]	Brazil	Observational study	162	Age, weight, HFNC flow	PICU	Escalation to noninvasive or invasive mechanical ventilation
Zayani et al., 2025 [17]	Tunisia	Prospective cohort	154	FiO_2, heart rate, Wang score	PICU	Escalation to noninvasive positive-pressure ventilation or invasive mechanical ventilation
Le Pallec et al., 2025 [18]	France	Multicenter retrospective cohort	383	ROX, age, prematurity	Seven pediatric/neonatal conventional or intermediate care units	Escalation to noninvasive or invasive ventilation

TABLE 1: Characteristics of the Included Studies

Abbreviations: HFNC, high-flow nasal cannula; ROX, respiratory rate–oxygenation index; ROX-HR, heart-rate-adjusted ROX; pCO_2, partial pressure of carbon dioxide; SpO_2, peripheral oxygen saturation; FiO_2, fraction of inspired oxygen; WDF, Wood-Downes-Ferrés score; mWCAS, modified Wood's Clinical Asthma Score.

Clinical Predictors of HFNC Failure

Several studies identified clinical characteristics associated with HFNC treatment failure in infants and young children with acute bronchiolitis. Abboud et al. [8] reported that infants who failed HFNC had

significantly lower body weight (p = 0.016) and higher respiratory rates before treatment initiation (p < 0.001). Kamit et al. [10] identified significant tachycardia, dehydration, and underlying chronic conditions as predictors of treatment failure among 84 patients, of whom 23 (27.3%) required escalation of respiratory support. D'Alessandro et al. [12] found that younger age (OR 1.12, 95% CI 1.03-1.23) and a Modified Tal score greater than five after four hours (OR 2.81, 95% CI 1.04-7.64) were independently associated with HFNC failure.

More recent studies reported similar associations between patient characteristics, clinical severity, and treatment outcomes. Westphal et al. [16] observed HFNC failure in 28 of 162 infants (17.3%), with younger age, lower weight, and lower initial HFNC flow associated with treatment failure. However, the Wood-Downes severity score was not independently significant in multivariable analysis. Zayani et al. [17] identified weight below the 10th percentile and a Wang clinical severity score of at least 10 at treatment initiation as predictors of failure. Overall, younger age, lower body weight, greater clinical severity, and persistent respiratory distress emerged as relevant clinical indicators, although the strength and consistency of these associations varied across studies.

Physiological Predictors of HFNC Failure

The included studies examined several physiological measures in relation to HFNC treatment failure, particularly respiratory rate, heart rate, oxygenation indices, and blood gas parameters. Milesi et al. [3] evaluated the ROX index and reported an AUC of 0.56 (95% CI 0.48-0.63) at baseline and 0.56 (95% CI 0.49-0.64) one hour after HFNC initiation. These findings indicate that ROX measurements obtained during the first hour provided limited discrimination between infants who subsequently required treatment escalation and those who responded successfully.

At 12 hours following HFNC initiation, Nascimento et al. [4] reported an ROX index AUC of 0.716 (95% CI 0.591-0.842; p = 0.016), indicating moderate discrimination between treatment success and failure. Etrusco Zaroni Santos et al. [15] similarly reported an ROX AUC of 0.70 (95% CI 0.54-0.84) at the same assessment time. In their analysis, the Wood-Downes-Ferrés score showed comparatively better discrimination (AUC 0.83, 95% CI 0.74-0.92), whereas the SpO_2/FiO_2 ratio had a lower AUC of 0.64 (95% CI 0.48-0.74).

Blood gas abnormalities and persistent physiological instability were also associated with treatment failure. Zayani et al. [17] identified an initial FiO_2 requirement of at least 42.5% and persistent tachycardia, tachypnea, hypercapnia, and FiO_2 of at least 48.5% after two hours as significant predictors. Overall, these findings suggest that physiological measurements obtained after HFNC initiation may provide useful prognostic information, although predictive accuracy varies according to the parameter and timing of assessment.

Clinical and Physiological Predictors of HFNC Failure

Across the included studies, clinical and physiological predictors of HFNC failure included younger age, lower body weight, increased respiratory rate, tachycardia, hypercapnia, clinical severity scores, and oxygenation indices. The predictive performance varied across studies and assessment time points. The major predictors and their reported findings are summarized in Table *2*.

Study	Predictor	Assessment Time	Reported Findings
Abboud et al., 2012 [8]	Respiratory rate, pCO_2, weight	Baseline	Higher respiratory rate and pCO_2 associated with failure ($p < 0.001$); lower weight ($p = 0.016$)
Guillot et al., 2018 [9]	pCO_2	Serial measurements	HR 1.37 per 5 mmHg increase (95% CI 1.01–1.87)
Kamit et al., 2020 [10]	Tachycardia, dehydration, pH	Baseline	Venous pH < 7.30, significant tachycardia, dehydration, and chronic conditions associated with failure; 23/84 patients (27.3%) failed HFNC
Nascimento et al., 2021 [11]	Respiratory rate, SpO_2	30 minutes / 6 hours	In the success group, respiratory rate decreased and SpO_2 increased within 30 minutes (both $p < 0.001$). Success and failure groups differed significantly at 6 hours (both $p < 0.01$); failure occurred in 18/83 patients (21.7%)
D'Alessandro et al., 2021 [12]	Age, Modified Tal score	Baseline / 4 hours	Age: OR 1.12 (95% CI 1.03–1.23); Tal score >5: OR 2.81 (95% CI 1.04–7.64)
Baquedano-Lobera et al., 2022 [13]	pCO_2, severity score	Baseline	pCO_2 ≥75 mmHg ($p = 0.043$) and higher bronchiolitis severity score ($p = 0.032$) predicted failure; 37/149 patients (24.8%) were nonresponders
Kannikeswaran et al., 2022 [14]	ROX index	Baseline	Lowest ROX quartile (≤5.39) versus highest (>8.21): adjusted OR 3.06 (95% CI 1.25–7.51; $p = 0.02$) for positive-pressure ventilation; AUROC 0.61 (95% CI 0.52–0.69)
Milesi et al., 2024 [3]	ROX index	Baseline / 1 hour	AUC 0.56 (95% CI 0.48–0.63) at baseline; AUC 0.56 (95% CI 0.49–0.64) at 1 hour
Nascimento et al., 2024 [4]	ROX index	12 hours	AUC 0.716 (95% CI 0.591–0.842)
Etrusco Zaroni Santos et al., 2024 [15]	ROX, WDF, SpO_2/FiO_2	12 hours	ROX AUC 0.70; WDF AUC 0.83; SpO_2/FiO_2 AUC 0.64
Westphal et al., 2025 [16]	Age, weight, HFNC flow	Baseline	Age ($p = 0.001$), weight ($p = 0.002$), disease severity ($p = 0.004$), and initial HFNC flow ($p = 0.001$) differed between groups; identified cutoffs: weight ≤5 kg, initial flow ≤12 L/min, Wood-Downes score ≥9
Zayani et al., 2025 [17]	FiO_2, Wang score, heart rate	Baseline / 2 hours	Weight below the 10th percentile, FiO_2 ≥42.5%, and Wang score ≥10 at initiation were predictors; persistent tachycardia, tachypnea, hypercapnia, and FiO_2 ≥48.5% after 2 hours were associated with failure; 54/154 patients (35.1%) failed HFNC
Le Pallec et al., 2025 [18]	ROX, age, prematurity	Baseline	ROX AUC 0.647; additional clinical factors evaluated

TABLE 2: Clinical and Physiological Predictors of HFNC Failure

Abbreviations: HFNC, high-flow nasal cannula; ROX, respiratory rate–oxygenation index; OR, odds ratio; HR, hazard ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval; WDF, Wood-Downes-Ferrés score; pCO_2, partial pressure of carbon dioxide; SpO_2, peripheral oxygen saturation; FiO_2, fraction of inspired oxygen.

Study-Specific ROX Index Performance and HFNC Failure Outcomes

The predictive performance of the ROX index at 12 hours after HFNC initiation was evaluated in two studies involving 228 participants. Nascimento et al. [4] reported an AUC of 0.716 (95% CI: 0.591-0.842) among 102 infants, whereas Etrusco Zaroni Santos et al. [15] reported an AUC of 0.70 (95% CI: 0.54-0.84) among 126 participants. Both studies demonstrated moderate discriminatory performance at 12 hours.

However, the studies differed in their definitions of HFNC treatment failure. Nascimento et al. [4] defined failure as escalation to noninvasive or invasive mechanical ventilation, reporting 18 failures among 102 infants (17.6%), including four who required invasive mechanical ventilation. In contrast, Etrusco Zaroni Santos et al. [15] defined failure as the requirement for invasive mechanical ventilation, with 29 of 126

infants (23.0%) requiring intubation. Because the outcomes represented different thresholds of respiratory support escalation, the failure proportions were reported separately without quantitative pooling to preserve clinical interpretability.

Risk-of-Bias Assessment

The methodological quality of the 13 included studies was evaluated using the QUIPS tool [6], covering six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. All 13 studies were assigned an overall moderate risk-of-bias judgment, as summarized in Table 3. The domain-level assessments revealed methodological concerns primarily related to participant selection, incomplete follow-up or outcome reporting, potential residual confounding, and variability in predictor assessment and statistical analysis.

Study	Participation	Attrition	Predictor Measurement	Outcome Measurement	Confounding	Statistical Analysis	Overall
Abboud et al., 2012 [8]	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Guillot et al., 2018 [9]	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Kamit et al., 2020 [10]	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Nascimento et al., 2021 [11]	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
D'Alessandro et al., 2021 [12]	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Baquedano-Lobera et al., 2022 [13]	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Kannikeswaran et al., 2022 [14]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Milesi et al., 2024 [3]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Nascimento et al., 2024 [4]	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Etrusco Zaroni Santos et al., 2024 [15]	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Westphal et al., 2025 [16]	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate
Zayani et al., 2025 [17]	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Le Pallec et al., 2025 [18]	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate

TABLE 3: Risk-of-Bias Assessment Using the QUIPS Tool

Abbreviation: QUIPS, Quality in Prognosis Studies.

Although several studies demonstrated low risk of bias in individual domains, all studies had at least one domain rated as moderate risk, particularly in relation to confounding. Consequently, no study was classified as having an overall low risk of bias. These findings suggest that the reported associations between clinical and physiological predictors and HFNC treatment failure should be interpreted cautiously, particularly where adjustment for potential confounders was limited or methodological reporting was incomplete. These methodological limitations were considered when interpreting the findings of the narrative synthesis, particularly in relation to variations in study designs, predictor measurements, and definitions of HFNC treatment failure.

Discussion

Principal Findings

This systematic review examined clinical and physiological predictors of HFNC treatment failure in infants and young children with acute bronchiolitis. The findings suggest that younger age, lower body weight, greater clinical severity, hypercapnia, persistent tachypnea, tachycardia, and increased oxygen requirements may be associated with treatment failure [8-13,16,17]. However, the strength and consistency of these associations varied across studies. The ROX index demonstrated limited discriminatory performance at baseline and one hour after HFNC initiation, whereas assessments at 12 hours showed moderate predictive accuracy [3,4,15]. These findings suggest that serial clinical assessment and physiological monitoring may

provide more useful prognostic information than isolated baseline measurements.

Comparison With Previous Studies

The findings are consistent with previous investigations highlighting the challenges of identifying reliable predictors of HFNC treatment failure. Abboud et al. [8] and Guillot et al. [9] reported associations between respiratory abnormalities, blood gas parameters, and treatment failure, while D'Alessandro et al. [12] emphasized the prognostic relevance of clinical severity assessment. More recent studies have examined the predictive performance of physiological indices, particularly the ROX index. Milesi et al. [3] reported limited discrimination at baseline and one hour, with AUC values of 0.56 at both time points. In contrast, Nascimento et al. [4] and Etrusco Zaroni Santos et al. [15] reported moderate discrimination at 12 hours, with AUC values of 0.716 and 0.70, respectively. These differences may reflect variations in patient characteristics, clinical severity, assessment timing, and definitions of treatment failure. An earlier systematic review also highlighted substantial heterogeneity and insufficient evidence to establish consistently reliable predictors [19].

Importantly, differences in the operational definitions of HFNC treatment failure limited direct comparisons across studies. Nascimento et al. [4] defined treatment failure as escalation to noninvasive or invasive mechanical ventilation, reporting 18 failures among 102 infants (17.6%), including four who required invasive mechanical ventilation. Conversely, Etrusco Zaroni Santos et al. [15] defined treatment failure in terms of invasive mechanical ventilation, reporting 29 events among 126 infants (23.0%). These outcomes represent different thresholds of respiratory support escalation and are not clinically equivalent. Consequently, the failure proportions were presented separately rather than quantitatively pooled. This approach preserves the clinical interpretation of the individual study findings and avoids generating a combined estimate from differently defined outcomes.

Clinical Implications

Early identification of infants at risk of HFNC treatment failure is essential for timely clinical reassessment and appropriate escalation of respiratory support. The findings suggest that clinicians should consider multiple parameters, including respiratory rate, heart rate, oxygen requirements, blood gas abnormalities, and clinical severity scores, rather than relying on a single predictor. Serial physiological assessment following HFNC initiation may help identify infants with persistent respiratory compromise. Although the ROX index provides an objective measure of respiratory status, its predictive performance varies with assessment timing and study-specific failure definitions. Therefore, it should not be used as the sole criterion for treatment escalation. Clinical judgment and ongoing monitoring remain essential, particularly in infants with worsening respiratory distress.

Strengths and Limitations

This systematic review provides a structured synthesis of available evidence regarding clinical and physiological predictors of HFNC treatment failure in infants and young children with acute bronchiolitis. An important strength is the evaluation of both baseline characteristics and serial physiological measurements, including respiratory rate, heart rate, blood gas parameters, clinical severity scores, oxygenation indices, and the ROX index. The inclusion of observational studies and secondary analyses of clinical trials provided evidence from different clinical settings. Furthermore, adherence to the PRISMA 2020 reporting framework and assessment of methodological quality using the QUIPS tool supported systematic reporting and critical appraisal of the included evidence.

Several limitations should be acknowledged. First, differences in study designs, sample sizes, patient characteristics, HFNC treatment protocols, predictor definitions, and assessment time points limited direct comparisons across studies. Many included studies were retrospective, introducing potential selection bias, residual confounding, and incomplete outcome reporting. Second, the lack of standardized definitions of HFNC treatment failure represented an important source of clinical heterogeneity. Some studies defined failure as escalation to noninvasive or invasive ventilation, whereas others considered invasive mechanical ventilation alone. These differences reflect distinct levels of respiratory deterioration and limit the comparability of reported failure proportions.

Third, heterogeneity in outcome definitions, predictor measurements, assessment intervals, and statistical adjustment methods precluded clinically meaningful quantitative pooling. Therefore, a narrative synthesis was considered the most appropriate approach for interpreting the available evidence. Additionally, only two studies reported ROX index discriminatory performance at 12 hours, and differences in their populations and failure definitions limited direct comparisons. Consequently, the evidence remains insufficient to establish universally applicable ROX thresholds or definitive prediction models. Further prospective multicenter studies using standardized definitions of HFNC treatment failure, consistent predictor assessment intervals, and transparent statistical reporting are needed to improve the reliability and clinical applicability of these findings.

Conclusions

Early identification of HFNC treatment failure in infants and young children with acute bronchiolitis is essential for timely clinical assessment and appropriate escalation of respiratory support. This systematic review identified younger age, lower body weight, greater clinical severity, hypercapnia, persistent tachypnea, tachycardia, and increased oxygen requirements as potential predictors of HFNC treatment failure, although the strength and consistency of these associations varied across studies. The ROX index demonstrated limited discriminatory performance at baseline and one hour after HFNC initiation, whereas moderate discrimination was reported at 12 hours in two studies. However, the available evidence remains insufficient to establish universally applicable ROX thresholds or support its use as an independent criterion for treatment escalation.

Differences in study populations, predictor assessment methods, and definitions of HFNC treatment failure limited direct comparability and precluded clinically meaningful quantitative pooling. Accordingly, findings were synthesized narratively, with emphasis on individual study results and their clinical interpretation. Overall, the evidence supports combining clinical evaluation with serial physiological monitoring rather than relying on a single predictive parameter. Further prospective multicenter studies using standardized definitions of HFNC treatment failure, consistent assessment intervals, and robust statistical methodologies are needed to validate predictive indicators and improve clinical decision-making.

Appendices

Supplementary material 1

Database	Complete Search Strategy	Records (n)
PubMed/MEDLINE	("Bronchiolitis"[MeSH Terms] OR bronchiolitis[tiab] OR "viral bronchiolitis"[tiab]) AND ("high-flow nasal cannula"[tiab] OR "high flow nasal cannula"[tiab] OR HFNC[tiab] OR "high-flow oxygen therapy"[tiab] OR "high flow oxygen"[tiab] OR "high-flow nasal oxygen"[tiab]) AND (fail*[tiab] OR predict*[tiab] OR "risk factor"[tiab] OR "risk factors"[tiab] OR escalation[tiab] OR "respiratory rate"[tiab] OR "heart rate"[tiab] OR oxygenation[tiab] OR hypercapnia[tiab] OR ROX[tiab] OR "severity score"[tiab])	318
Embase (Embase.com)	('bronchiolitis'/exp OR bronchiolitis:ti,ab,kw) AND ('high flow nasal cannula':ti,ab,kw OR 'high-flow nasal cannula':ti,ab,kw OR hfnc:ti,ab,kw OR 'high flow oxygen therapy':ti,ab,kw OR 'high flow nasal oxygen':ti,ab,kw) AND (fail*:ti,ab,kw OR predict*:ti,ab,kw OR 'risk factor':ti,ab,kw OR 'risk factors':ti,ab,kw OR escalation:ti,ab,kw OR 'respiratory rate':ti,ab,kw OR 'heart rate':ti,ab,kw OR hypercapnia:ti,ab,kw OR oxygenation:ti,ab,kw OR rox:ti,ab,kw)	402
Scopus	TITLE-ABS-KEY(bronchiolitis OR "viral bronchiolitis") AND TITLE-ABS-KEY("high-flow nasal cannula" OR "high flow nasal cannula" OR HFNC OR "high-flow oxygen therapy" OR "high-flow nasal oxygen") AND TITLE-ABS-KEY(fail* OR predict* OR "risk factor" OR "risk factors" OR escalation OR "respiratory rate" OR "heart rate" OR hypercapnia OR oxygenation OR ROX)	279
Web of Science Core Collection	TS=(bronchiolitis OR "viral bronchiolitis") AND TS=("high-flow nasal cannula" OR "high flow nasal cannula" OR HFNC OR "high-flow oxygen therapy" OR "high-flow nasal oxygen") AND TS=(fail* OR predict* OR "risk factor" OR "risk factors" OR escalation OR "respiratory rate" OR "heart rate" OR hypercapnia OR oxygenation OR ROX)	201
Cochrane Library	#1 MeSH descriptor: [Bronchiolitis] explode all trees #2 bronchiolitis:ti,ab,kw #3 #1 OR #2 #4 ("high-flow nasal cannula" OR "high flow nasal cannula" OR HFNC OR "high-flow oxygen therapy" OR "high-flow nasal oxygen"):ti,ab,kw #5 (fail* OR predict* OR "risk factor" OR "risk factors" OR escalation OR "respiratory rate" OR "heart rate" OR oxygenation OR hypercapnia OR ROX):ti,ab,kw #6 #3 AND #4 AND #5	86
Total database records		1,286

TABLE 4: Database Search Strategy and Records Identified

Supplementary material 2

Additional Source	Search Approach / Methodology	Records (n)
Google Scholar	Search using combinations of “HFNC,” “high-flow nasal cannula,” “bronchiolitis,” “treatment failure,” and “clinical predictors.” Potentially relevant titles and abstracts were identified for eligibility assessment.	46
Reference List Screening	Reference lists of relevant primary studies and systematic reviews were examined manually to identify additional potentially eligible studies on clinical and physiological predictors of HFNC failure in infants with bronchiolitis.	20
Forward Citation Tracking	Articles citing relevant primary studies on HFNC failure predictors were examined to identify additional publications potentially meeting the eligibility criteria.	6
Total Additional Records		72

TABLE 5: Supplementary Search Methods and Records Identified

Supplementary material 3

PRISMA Stage	Screening Details	Records/Reports (n)
Identification		
	PubMed/MEDLINE	318
	Embase	402
	Scopus	279
	Web of Science	201
	Cochrane Library	86
	Total database records identified	1,286
	Google Scholar	46
	Reference list screening	20
	Forward citation tracking	6
	Total additional records identified	72
	Total records identified	1,358
Screening		
	Duplicate database records removed	321
	Database records screened (titles and abstracts)	965
	Records excluded during screening	884
Eligibility Assessment — Database Sources		
	Database reports sought for retrieval	81
	Reports not retrieved	0
	Database full-text reports assessed	81
	Database reports excluded	73
	Wrong population	21
	Age over 24 months / no separate subgroup data	16
	No relevant outcome	14

	No relevant predictors evaluated	10
	Insufficient numerical data	6
	Duplicate/overlapping/non-original study	5
	Broader outcome definition not suitable	1
Eligibility Assessment — Additional Sources		
	Additional-source reports sought for retrieval	72
	Reports not retrieved	0
	Additional-source full-text reports assessed	72
	Additional-source reports excluded	67
	Wrong population	18
	Age over 24 months / no separate subgroup data	15
	No relevant outcome	13
	No relevant predictors evaluated	9
	Insufficient numerical data	6
	Duplicate/overlapping/non-original study	5
	Broader outcome definition not suitable	1
Overall Eligibility		
	Total reports assessed for eligibility	153
	Total full-text reports excluded	140
Included Studies		
	Studies included in systematic review	13
	Reports of included studies	13

TABLE 6: Summary of Study Identification and Screening According to PRISMA 2020

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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