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ORIGINAL ARTICLE

Nasal Continuous Positive Airway Pressure versus High-flow Nasal Cannula in Infants with Respiratory Distress Syndrome: a Systematic Review of Randomized Clinical Trials

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a leading cause of respiratory failure in preterm infants, primarily resulting from surfactant deficiency and alveolar collapse. Approximately 15%–20% of affected children require respiratory support. Despite advances in antenatal care and non-invasive ventilation that have reduced mortality and complications, the optimal mode of respiratory support remains uncertain. Nasal continuous positive airway pressure (NCPAP) and high-flow nasal cannula (HFNC) are among the most widely used non-invasive methods for managing RDS—NCPAP enhances lung expansion and oxygenation, while HFNC offers greater comfort and ease of application. Given the ongoing debate over their relative efficacy and safety, this study aimed to systematically review and compare HFNC and NCPAP as initial respiratory support strategies in preterm infants with RDS.

Methods: This systematic review was conducted in accordance with PRISMA guidelines. A comprehensive literature search of PubMed, Web of Science, and Scopus was performed to identify studies published between 2015 and 2025 comparing NCPAP with HFNC in preterm or term infants diagnosed with respiratory distress syndrome. Randomized controlled trials and eligible observational studies reporting at least one relevant clinical outcome were considered. Following duplicate removal, titles and abstracts were screened, and potentially relevant articles were assessed for full-text eligibility. Of 565 records identified, 336 were screened, and 12 studies met the inclusion criteria and were included in the final qualitative synthesis.

Results: Twelve published studies, conducted between 2017 and 2022, with a total of 1,242 patients, were included. The studies, including preterm infants with respiratory distress, were analyzed. HFNC demonstrated comparable efficacy to NCPAP in terms of respiratory outcomes, including respiratory distress syndrome, bronchopulmonary dysplasia, need for invasive mechanical ventilation, and treatment failure. HFNC was associated with reduced nasal trauma and, in some studies, faster achievement of full enteral feeding. Trends toward shorter non-invasive ventilation duration and hospital stay were observed, but were not consistently statistically significant.

Conclusion: HFNC is a safe and generally effective alternative to NCPAP for preterm infants with respiratory distress, particularly those over 28 weeks' gestation. HFNC offers advantages in comfort, ease of use, and reduced nasal injury, with similar respiratory outcomes and complication rates compared to NCPAP. Evidence is less clear for extremely low-birth-weight infants, highlighting the need for larger trials to guide optimal use.

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Introduction

Bronchiolitis is the leading cause of respiratory distress in infants under 1 year old who are admitted to the hospital. Previous research indicated that bronchiolitis accounts for 17.1% of all urgent admissions to pediatric intensive care units and is a major cause of mortality and morbidity in preterm neonates, placing a significant strain on healthcare resources [1,2]. As well, about 15% to 20% of children who are affected need respiratory assistance and intensive care because they quickly develop breathing difficulties [3].

The latest recommendations for treating infants with bronchiolitis or other forms of respiratory distress in hospital settings highlight the critical role of oxygen therapy, respiratory assistance, and ensuring proper hydration in cases of hypoxia [4]. Managing patients, especially infants, experiencing respiratory distress, presents a significant challenge for pediatricians in primary care [5]. Timely and effective management is essential to prevent fatalities, minimize the risk of long-term disabilities, and reduce healthcare costs. Once respiratory distress has been identified, treatment should focus first on ensuring proper oxygenation, followed by diagnosing the root causes and any potential complications [1].

In preterm infants, the lungs are immature, and the system responsible for surfactant production is underdeveloped. Respiratory distress syndrome (RDS) mainly results from insufficient surfactant production, leading to difficulty in exchanging oxygen and carbon dioxide by alveoli [6]. Primarily, this difficulty could lead to alveolar collapse, impaired gas exchange, and respiratory failure. Surfactant is a complex mixture of phospholipids and proteins produced by type II alveolar cells. The resulting alveolar collapse due to insufficient surfactant production causes leakage of plasma proteins into alveoli, forming a hyaline membrane that reduces oxygen diffusion. This dysfunction overloads the lungs during breathing and results in progressive hypoxemia and respiratory acidosis in preterm infants [7].

Most premature infants born before 30 weeks of gestation possess underdeveloped lungs, and almost half of these infants continue to require surfactant treatment [8]. Improvements in preventing and managing RDS include the use of medications to avert premature births and promote lung development, the replacement of surfactants, and the adoption of innovative mechanical ventilation methods [9]. These advancements are expected to further reduce both death rates and complications linked to this condition [6].

High-flow nasal cannula (HFNC) and nasal continuous positive airway pressure (NCPAP) are the most frequently utilized forms of non-invasive respiratory assistance for premature infants and newborns, for children suffering from bronchiolitis and other underlying causes [10]. Previous research has investigated the effectiveness of HFNC therapy, while other studies have examined the use of continuous positive airway pressure (CPAP), which is noted for its capacity to enhance functional residual capacity and decrease the frequency of apneic episodes [11-13].

HFNC oxygen therapy delivers warm, humidified oxygen at a flow rate exceeding typical inspiratory flow rates. Research indicates that it may be effective in enhancing oxygen levels and reducing the need for mechanical ventilation in pediatric patients experiencing respiratory distress [14-16]. NCPAP represents a treatment option that can be challenging in resource-limited environments, often necessitating technical expertise and proper upkeep [17,18].

Methodology

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A detailed review protocol was developed before searching and is available upon request. To identify relevant studies, a comprehensive literature search was performed across multiple electronic databases within the last 10 years (2015 to 2025), including PubMed, Web of Science, and Scopus. The search utilized the following keywords: ((“Respiratory Distress Syndrome” OR RDS OR “Hyaline Membrane Disease” OR “neonatal respiratory failure” OR “neonatal respiratory distress”) AND (infant* OR newborn* OR neonat* OR preterm OR prematur*)) AND ((“Continuous Positive Airway Pressure” OR CPAP OR “nasal cpap” OR nCPAP OR “nasal continuous positive airway pressure”) AND (“High-Flow Nasal Cannula” OR HFNC OR “high flow oxygen” OR “high flow therapy” OR “nasal high flow” OR NHF)).

Eligibility criteria

Inclusion criteria

Studies were included if they met the following inclusion criteria:

1. Assessed the use of HFNC and CPAP as a respiratory support in infants diagnosed with RDS.
2. Included the pediatric population, the preterm infants age group.
3. Reported clinical outcomes: safety and efficacy outcomes.
4. Employed RCTs in English-language publications between 2015 and 2025.

Exclusion criteria

Studies were excluded if they:

1. Included infants with other respiratory diseases.
2. Included different age groups (adults or older pediatric populations).
3. Were reviews, meta-analyses, commentaries, letters, or had insufficient reported data.

Selection of articles and data extraction

After the initial database search, two reviewers independently screened the titles and abstracts to identify relevant studies based on predefined inclusion criteria.

Full texts of selected articles were assessed for eligibility by the same reviewers, with disagreements resolved through discussion or consultation with a third reviewer. Data were extracted using a standardized form, including study characteristics (author, year, design, country), patient demographics (total sample size, mean age and range, gender distribution, gestational age, birthweight, apgar score, and antenatal steroids), intervention details (NCPAP vs. HFNC and their adjustments), safety, and efficacy outcomes.

Quality assessment

The Cochrane risk-of-bias tool for randomized trials (RoB2) [19] was used to assess the risk of bias (RoB) in the studies. It evaluates the potential for bias in randomized controlled trials (RCTs) by examining five critical areas: randomization, deviations from planned interventions, handling of missing data, outcome measurement, and the selection of reported outcomes. Each area is classified as having low, some, or high RoB, and the overall bias risk for each study is established based on these evaluations.

Results

PRISMA diagram

The literature search identified a total of 565 records across the selected databases. After removal of 229 duplicate records, 336 unique records were screened based on titles and abstracts, resulting in the exclusion of 302 records that did not meet the predefined eligibility criteria. The remaining 34 articles underwent full-text assessment for eligibility. Of these, 22 studies were excluded for the following reasons: inaccessible full text (n = 5), incompatible study design (n = 5), population-related issues (n = 4), irrelevant outcomes (n = 5), and language restrictions (n = 3). Ultimately, 12 studies fulfilled all inclusion criteria and were included in the final qualitative synthesis (Figure 1).

Table 1 describes the included studies on the use of NCPAP versus HFNC in infants with RDS, highlighting several key features. The evidence base primarily consists of RCT studies. This table presents baseline characteristics, including study design, country, sample size, gender distribution, neonatal clinical parameters, and maternal factors. By organizing these details, the table shows both controlled efficacy data and real-world clinical outcomes, allowing comparison across studies and ensuring transparency in study populations and methodologies.

Table 2 summarizes the intervention protocols used in the included studies, including FiO_2 ranges, oxygen saturation targets, flow/pressure settings, and interface types for both CPAP and HFNC.

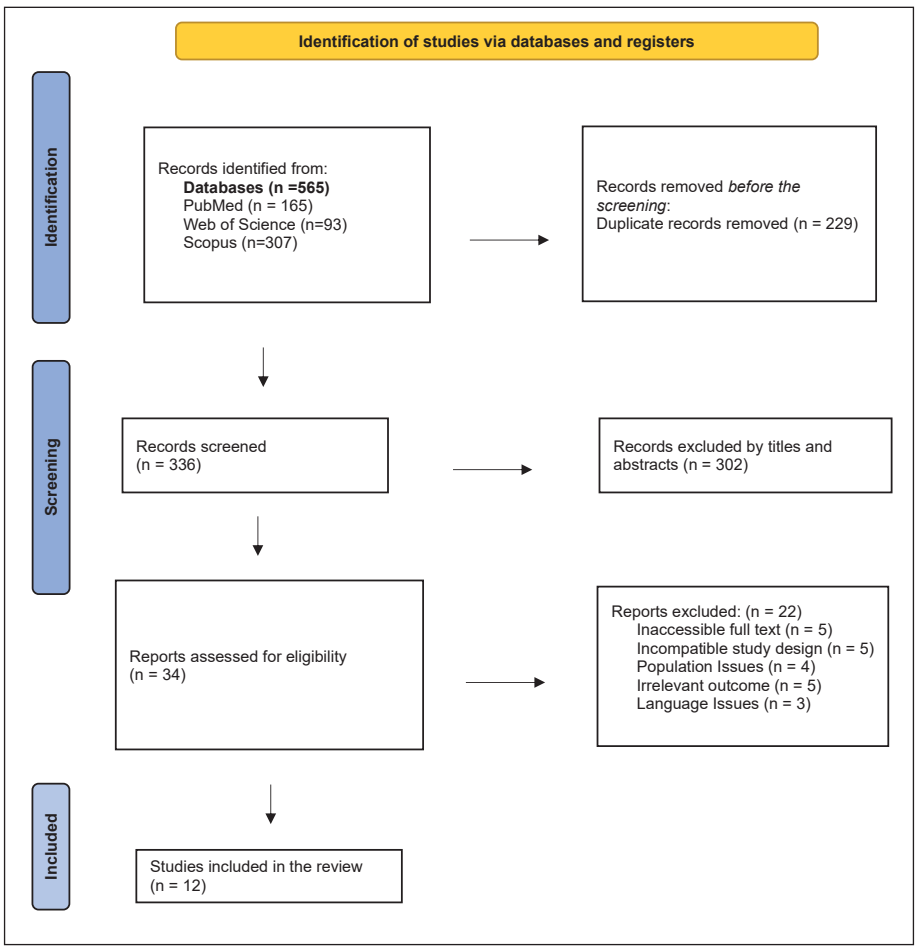

Figure 1. *Schematic representation of the criteria for choosing included studies.*

Table 1. *Characteristics of studies included in the review (NCPAP vs. HFNC in infants with RDS).*

Author, Year	Study Design, Country	Total Sample Size	Gender (M/F)	Gestational Age (mean ± SD)	SGA (mean ± SD)	LGA (mean ± SD)	Birthweight (mean ± SD)	Apgar Score median (IQR)	Antenatal Steroid Use
Grover et al. 2022 [20]	Non-inferiority RCT India	124 63 NCPAP / 61 HFNC	NCPAP: 27 (42.9) F HFNC: 32 (52.5) F	NCPAP: 33.0 (2.27) HFNC: 33.3 (2.13)	NCPAP: 22 (34.9) HFNC: 23 (37.7)	NCPAP: 3 (4.8) HFNC: 1 (1.6)	NCPAP: 1,778 (575) HFNC: 1,844 (539)	1 minute: NCPAP: 7 (6-8), HFNC: 8 (7-8) 5 minutes: NCPAP: 9 (8-9), HFNC: 9 (8-9)	NCPAP: 32/33 (96.9) HFNC: 30/30 (100)
Singh et al. 2022 [21]	Non-inferiority RCT India	30 15 NCPAP / 15 HFNC	NCPAP: 6 M HFNC: 9 M	NCPAP: 30 weeks (1.8) HFNC: 31 weeks (2.1)	NR	NR	NCPAP: 1,440.7 (293.8) HFNC: 1,478.4 (289.6)	NR	NCPAP: 13 HFNC: 12
Demirel et al. 2021 [22]	Prospective RCT Turkey	107 54 CPAP / 53 HFNC	CPAP: 25 (46.2) F HFNC: 23 (43.3) F	CPAP: 31.0 (1.8) HFNC: 31.2 (2.3)	NR	NR	CPAP: 1,505 (580) HFNC: 1,570 (455)	NR	CPAP: 40 (74) HFNC: 38 (71.6)
Chen et al. 2020 [23]	RCT China	94 46 CPAP / 48 HFNC	CPAP: 29/17 HFNC: 30/18	CPAP: 27.5 ± 3.2 HFNC: 27.2 ± 2.8	CPAP: 8 (17.39) HFNC: 9 (18.75)	NR	CPAP: 794 ± 31.0 HFNC: 827 ± 23.0	1 minute: CPAP: 5.4 ± 0.4, HFNC: 5.2 ± 0.6	CPAP: 36 (78.26) HFNC: 38 (79.17)
Charki et al. 2020 [24]	Non-inferiority trial India	106 52 NCPAP / 54 HFNC	NCPAP: 36/16 HFNC: 39/15	28-34 weeks: NCPAP: 30, HFNC: 20 34-37 weeks: NCPAP: 18, HFNC: 30	NR	NR	1-1.5 kg: NCPAP:10, HFNC:9 1.5-2.5: NCPAP:34, HFNC:40 >2.5: NCPAP:5, HFNC:3	NR	NCPAP: 3 HFNC: 4
Akbarian-rad et al. 2020 [25]	RCT Iran	64 32 NCPAP / 32 HFNC	NCPAP: 15/19 HFNC: 13/17	NCPAP: 30.98 ± 1.83 HFNC: 30.45 ± 2.00	NR	NR	NCPAP: 1,348.97 ± 334.71 HFNC: 1416.00 ± 493.26	NR	NCPAP: 19 (55.9) HFNC: 23 (76.7)
Armanian et al. 2019 [26]	RCT Iran	72 37 NCPAP / 35 HFNC	NR	NR	NR	NR	NR	NR	NR
Skariah et al. 2019 [27]	Prospective study India	84 27-32 weeks: 22 NCPAP / 15 HFNC 33-36 weeks: 21 NCPAP / 26 HFNC	27-32 weeks: NCPAP: 9/13, HFNC: 9/6 33-36 weeks: NCPAP: 12/9, HFNC: 17/9	27-32 weeks: NCPAP: 30.7 ± 1.31, HFNC: 30.8 ± 1.45 33-36 weeks: NCPAP: 33.72 ± 1.7, HFNC: 34.7 ± 1.00	NR	NR	27-32 weeks: NCPAP:1,342 ± 318, HFNC:1,413 ± 311 33-36 weeks: NCPAP:1,898 ± 463, HFNC:2,396 ± 512	NR	27-32 weeks: NCPAP: 21/22, HFNC: 9/15 33-36 weeks: NCPAP: 6/11, HFNC: 11/26
Murki et al. 2018 [28]	RCT India	272 139 NCPAP / 133 HFNC	NCPAP: 77 (55%) M HFNC: 73 (55%) M	NCPAP: 31.6 ± 2.2 HFNC: 31.8 ± 1.9	NR	NR	NCPAP: 1,642 ± 437 HFNC: 1,632 ± 431	1 minute: NCPAP:7(6-7), HFNC:7(6-7) 5 minuites: NCPAP:8 (7-8), HFNC:8 (7-8)	Complete: NCPAP:78 (56), HFNC:83 (62) Partial: NCPAP:40 (29), HFNC:34 (26)
Farhat et al. 2018 [29]	RCT Iran	160 53 NCPAP / 53 NIPPV / 54 HFNC	NCPAP: 64.2% M HFNC: 61.1% M	NCPAP: 31.1 (2) HFNC: 31.3 (1.9)	NR	NR	NCPAP: 1,650 (486) HFNC: 1,624 (425)	1 minute: NCPAP:6.4, HFNC:6.9 5 minutes: NCPAP:7.7, HFNC:8.0	NCPAP: 83% HFNC: 88.9%

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Author, Year	Study Design, Country	Total Sample Size	Gender (M/F)	Gestational Age (mean ± SD)	SGA (mean ± SD)	LGA (mean ± SD)	Birthweight (mean ± SD)	Apgar Score median (IQR)	Antenatal Steroid Use
Shin et al. 2017 [30]	RCT non-inferiority Korea	85 43 NCPAP / 42 HFNC	NCPAP: 24 (55.8%) M HFNC: 23 (54.8%) M	NCPAP: 33.0 ± 1.2 HFNC: 32.5 ± 1.5	NR	NR	NCPAP: 1,996 ± 374 HFNC: 2,058 ± 371	1 minute: NCPAP:7 (5-8), HFNC:7 (6-8) 5 minutes: NCPAP:9 (8-9), HFNC:9 (8-9)	NCPAP: 23 (53.5) HFNC: 27 (64.3)
Glackin et al. 2017 [31]	Single-center RCT Ireland	44 22 CPAP / 22 HFNC	NR	NCPAP: 27.3 ± 1.5 HFNC: 26.9 ± 1.5	NR	NR	NCPAP: 891 ± 202 HFNC: 868 ± 160	1 minute: NCPAP:5 (4-6), HFNC:6 (5-7) 5 minutes: NCPAP:8 (6-8), HFNC:8 (7–8)	NCPAP: 86 HFNC: 77

CPAP, Continuous Positive Airway Pressure, F, Female, HFNC, High-Flow Nasal Cannula, IQR, Interquartile Range, LGA, Large for Gestational Age, M, Male, NCPAP, Nasal Continuous Positive Airway Pressure, NIPPV, Nasal Intermittent Positive Pressure Ventilation, NR, Not Reported, RCT, Randomized Controlled Trial, SD, Standard Deviation, SGA, Small for Gestational Age, WKS, Weeks.

Table 3 compiles the primary and secondary outcomes reported in the studies, covering treatment success/failure, mortality, comorbidities, adverse events, and the need for escalation of care.

We considered the RoB when interpreting findings, as shown in Table 4.

The RoB across the 12 included studies was generally "low" to "some concerns" (Figure 2). Singh et al. [21] display low RoB across all key domains, indicating a rigorous design and conduct with proper randomization, adherence to interventions, complete outcome data, reliable measurements, and transparent reporting. Most studies demonstrated a low RoB in outcome measurement and reporting (Domains 4 and 5). However, concerns were noted in randomization procedures and deviations from intended interventions (Domains 1 and 2) in several studies. In particular, three studies [22, 28] were judged to have a high overall RoB, mainly due to issues with randomization or missing outcome data. These limitations should be considered when interpreting the pooled evidence.

Discussion

This systematic review of 12 studies involving preterm infants with respiratory distress indicates that HFNC is a safe and effective alternative to NCPAP. In infants over 28 weeks' gestation, HFNC demonstrated comparable efficacy to NCPAP regarding key respiratory outcomes, including RDS, BPD, duration of non-invasive ventilation, and need for invasive mechanical ventilation. Additional advantages, such as ease of use, patient comfort, and suitability for the delivery room, make HFNC a viable first-line or alternative non-invasive ventilation strategy when NCPAP is unavailable. Some studies further suggested potential benefits in shorter hospital stays and reduced non-invasive ventilation duration, though these results were not always statistically significant.

Consistent with our review, the included study observed no statistically significant differences between HFNC and NCPAP in demographic characteristics, respiratory outcomes, or complications such as NEC, BPD, pneumothorax, and mortality. Although the HFNC group showed trends toward shorter hospitalization, reduced intubation, and decreased need for full nutritional and oxygen support, these differences were not statistically significant, supporting the general conclusion that HFNC is a safe and effective alternative to NCPAP [19].

Similar to the studies included in this review, a trial involving 120 preterm neonates (51 males, 69 females) found no statistically significant differences between HFNC and NCPAP in major clinical outcomes, including NEC, IVH, pneumothorax, chronic lung disease, treatment failure, and mortality. Additionally, GA, birth weight, Apgar scores, RDS severity, and duration of oxygen therapy and hospitalization were comparable between groups. Notably, the HFNC group experienced a lower incidence of nasal trauma, although they required more surfactant therapy and had a longer duration of intervention. These findings are consistent with the overall evidence that HFNC is a safe and generally

Table 2. *Intervention parameters: Nasal CPAP and HFNC.*

Author, Year	HFNC FiO_2	HFNC SpO_2	HFNC Pressure and/or Flow	HFNC Interface	CPAP Pressure and/or Flow	CPAP FiO_2	CPAP SpO_2	CPAP Interface
Grover et al. 2022 [20]	21% (21-25)	90%-94%	4 l/minute up to 8 l/minute	NR	5 cm H_2O up to 8 cm	21% (21-25)	90%-94%	Binasal prongs
Singh et al. 2022 [21]	60%	91%-95%	2 l/minute up to 8 l/minute	NR	5 cm H_2O up to 7 cm	60%	91%-95%	Nasal prongs
Demirel et al. 2021 [22]	≤28 weeks: 40% (45) >28 weeks: 30% (20)	90%-95%	6 l/minute up to 8 l/minute	NR	6 cm H_2O	≤28 weeks: 40% (7.5) >28 weeks: 40% (12.5)	90%-95%	Binasal prongs
Chen et al. 2020 [23]	30%-40%	NR	4–6 l/minute	NR	Flow 6-8 l/minute	40%	NR	NR
Charki et al. 2020 [24]	21%-40%	NR	Weight-based (2 l/kg)	Nasal prongs	Flow 5-8 l/minute	21–40%	NR	Binasal midline prongs
Akbarian-rad et al. 2020 [25]	Up to 40%	NR	3–5 l/minute	Short binasal prongs	5 cm H_2O	30%	NR	Face mask
Armanian et al. 2019 [26]	>30%	<91%	<1,000 g: 2.5 l/minute 1,000-1,500 g: 3 l/minute Temp: 37°C	Nasal cannula 2 mm + oxygen interface & warm humidifier	5-6 cm H_2O Flow 8-10 l/minute	>30%	<91%	Nasal prongs + joints
Skariah et al. 2019 [27]	Adjusted per protocol	Adjusted per protocol	Flow 8 l/minute (initial)	Nasal cannula	5 cm H_2O	Adjusted per protocol	Adjusted per protocol	Nasal mask
Murki et al. 2018 [28]	50% (30-50)	Target 90%–95%	Flow 5 l/minute	Nasal prongs	5 cm H_2O	40% (30-50)	Target 90%-95%	Short binasal prongs
Farhat et al. 2018 [29]	Adjusted per O_2 need	Not specified	≥2 l/minute (weight-based) up to 5 l/minute	Humidified HFNC	Initial 6 cm H_2O up to 8 cm H_2O	Adjusted per O_2 need	Not specified	Nasal prongs/mask with CPAP system
Shin et al. 2017 [30]	Start 0.40; wean → 0.25 → 0.21	Target 88%–94%	Initial 5 l/minute adjusted 3-7 L/minute wean at 3 l/minute	Short binasal prongs	4-7 cm H_2O (guided by blood gas)	Start 0.40; wean → 0.25 → 0.21	Target 88%-94%	Short binasal prongs

cm H_2O, Centimeters of Water, CPAP, Continuous Positive Airway Pressure, FiO_2, Fraction of Inspired Oxygen, HFNC, High-Flow Nasal Cannula, H_2O, Water, l/minute, Liters per Minute, NR, Not Reported, SpO_2, Peripheral Oxygen Saturation, Temp, Temperature.

Table 3. *Reported efficacy and safety outcomes.*

Author, Year	Tx Failure 24 hours, n (%)	Failure of Assigned Support (N)	Causes of Tx Failure at 24 hours	Tx Failure 72 hours, n (%)	Comorbidities	MV within 72 hours, n (%)	Surfactant Admin. (n/%)	Caffeine (n/%)	Conclusion
Grover et al. 2022 [20]	NCPAP: 7 (11.1) HFNC: 8 (13.1)	NR	Apnea: NCPAP:2 (28.6), HFNC:1 (12.5) FiO_2≥0.4: NCPAP:3 (42.9), HFNC:6 (75) ABG: NCPAP:1 (14.3), HFNC:1 (12.5)	NCPAP: 11 (17.5) HFNC: 10 (16.4)	NR	NCPAP: 11 (17.5) HFNC: 7 (11.5)	HFNC: 71 (56.8)	NCPAP: 25 (39.7)	HFNC is effective and safe for respiratory stabilization in preterm infants >28 wks' gestation. Non-inferiority to NCPAP remains unclear. Larger multicentric studies needed.
Singh et al. 2022 [21]	NR	NR	NR	NR	IVH: NCPAP:4, HFNC:3 BPD: NCPAP:4 ROP: NCPAP:3, HFNC:1 Sepsis: NCPAP:6, HFNC:5 Hs-PDA: NCPAP:12, HFNC:12	NR	NCPAP: 5 (7.9) HFNC: 18 (29.5)	NR	HFNC at least as effective as NCPAP for preterm infants >28 wks with RDS following INSURE.
Demirel et al. 2021 [22]	NR	NR	NR	NR	PDA: NCPAP:6 (11.1%), HFNC:5 (9.4%) Sepsis: NCPAP:7 (12.9%), HFNC:6 (11.3%) IVH: NCPAP:1 (1.8%), HFNC:2 (3.7%) NEC: NCPAP:1 (1.8%), HFNC:1 (1.8%) ROP: NCPAP:1 (1.8%), HFNC:2 (3.7%) BPD(≤28 wks): NCPAP:6 (75%), HFNC:2 (28.5%) Pneumothorax(>28 wks): NCPAP:1, HFNC:2	NR	HFNC: 4 (6.6) NCPAP: 15	NR	No significant differences in weaning time, RDS, BPD, hospital stay, or complications between HFNC and CPAP as primary respiratory support.
Chen et al. 2020 [23]	NR	NR	NR	NR	ICH: NCPAP:7 (15.21), HFNC:7 (14.58) ROP: NCPAP:18 (39.13), HFNC:17 (35.42) PDA: NCPAP:16 (34.78), HFNC:16 (33.33) BPD: NCPAP:15 (32.61), HFNC:16 (33.33) NEC: NCPAP:13 (28.26), HFNC:5 (10.42) Nasal injury: NCPAP:17 (36.96), HFNC:3 (6.25)	NR	NR	HFNC: 14	HFNC more effective than NCPAP in preventing extubation failure in preterm ELBWI. Reduces O_2 use time, nasal injury, NEC, LOS, and costs.
Charki et al. 2020 [24]	NR	NCPAP: 3 HFNC: 5	NR	NR	ROP: NCPAP:2 (3.8%), HFNC:2 (3.7%) IVH: NCPAP:2 (3.8%), HFNC:2 (3.7%) Nosocomial infection: NCPAP:8 (15.4%), HFNC:8 (14.8%) NEC: NCPAP:13 (25%), HFNC:1 (1.9%) Nasal trauma: NCPAP:30 (57.7%), HFNC:1 (1.9%)	NR	NCPAP: 2 HFNC: 1	NR	HFNC had fewer nasal injuries and NEC, and reached full feeding faster. Noninferior to NCPAP; safe and effective for preterm infants.

Continued

Author, Year	Tx Failure 24 hours, n (%)	Failure of Assigned Support (N)	Causes of Tx Failure at 24 hours	Tx Failure 72 hours, n (%)	Comorbidities	MV within 72 hours, n (%)	Surfactant Admin. (n/%)	Caffeine (n/%)	Conclusion
Akbarian-rad et al. 2020 [25]	NR	NCPAP: 4 (11.8%) HFNC: 5 (16.7%)	NR	NR	Pneumothorax: NCPAP:2, HFNC:2 IVH: NCPAP:2, HFNC:3	NR	NR	NR	HFNC comparably effective to NCPAP for RDS after surfactant. Suitable alternative when NCPAP unavailable, with similar failure rate.
Armanian et al. 2019 [26]	NR	NCPAP: 13 (35.1) HFNC: 19 (54.3)	Hypoxia (FiO□≥40%): NCPAP:5 (38.4), HFNC:14 (73.6) Resp. acidosis: NCPAP:2 (15.4), HFNC:1 (5.3) Urgent intubation: HFNC:1 (5.3) Apnea: NCPAP:3 (23.1), HFNC:3 (15.8)	NR	IVH: NCPAP:5 (13.5), HFNC:1 (2.9) PDA: NCPAP:8 (21.6), HFNC:10 (28.6) Pneumothorax: NCPAP:5 (13.5), HFNC:2 (5.7)	NR	NCPAP: 26 (70.3) HFNC: 22 (62.9)	NR	HFNC as initial tx for VLBW preterm infants with RDS is associated with higher failure rates than NCPAP. Should not be considered primary treatment.
Skariah et al. 2019 [27]	NR	27-32 weeks: NCPAP:5/22 (22.7), HFNC:4/15 (26.7) 33-36 weeks: NCPAP:2/21 (9.5), HFNC:2/26 (7.7)	NR	NEC - 27-32 weeks: NCPAP:nil, HFNC:1/15 33-36 weeks: HFNC:1/26 IVH - 27-32 weeks: NCPAP:1/22, HFNC:3/15 33-36 weeks: NCPAP:0, HFNC:1/26 ROP - 27-32 weeks: NCPAP:3/22, HFNC:2/15 33-36 weeks: NCPAP:0, HFNC:1/26	NR	NR	INSURE: 27-32 weeks: NCPAP:9/22, HFNC:4/15 33-36 weeks: HFNC:1/25	NR	HFNC shows similar clinical efficacy/safety to NCPAP and shorter NIV duration. Does not lower MV need in first 72 hours. More trials needed.
Murki et al. 2018 [28]	NR	NR	↑O_2: NCPAP:3/11 (27), HFNC:16/35 (46) ↑RD: NCPAP:4/11 (36), HFNC:14/35 (40) Apnea: NCPAP:3/11 (27.3), HFNC:3/35 (8.6) Other: NCPAP:1/11 (9.1), HFNC:2/35 (5.6)	NCPAP:11 (7.9), HFNC:35 (26.3) SAS>5: NCPAP:6/64 (9.4), HFNC:21/54 (38.9) SAS≤5: NCPAP:5/75 (6.7), HFNC:14/79 (17.7) <32 wks: NCPAP:7/68 (10.3), HFNC:22/58 (37.9) ≥32 wks: NCPAP:6/71 (8.5), HFNC:15/75 (20.0)	Pneumothorax: NCPAP:1 (0.7) HS-PDA: NCPAP:13 (9.4), HFNC:8 (6.0) Sepsis: NCPAP:13 (9.4), HFNC:13 (9.8) NEC≥IIo: HFNC:2 (1.5) Nasal injury: NCPAP:13 (9.4), HFNC:7 (5.3) ROP: NCPAP:7 (5.0), HFNC:6 (4.5)	Within 3 days: NCPAP:11 (7.9), HFNC:8 (6.0) Within 7 days: NCPAP:13 (9.4), HFNC:9 (6.8)	Dose 1: NCPAP:68 (48.9), HFNC:58 (43.6) Dose 2: NCPAP:24 (17.3), HFNC:18 (13.5)	NR	HFNC less effective than NCPAP at preventing need for higher respiratory support within the first 72 h.

Continued

Author, Year	Tx Failure 24 hours, n (%)	Failure of Assigned Support (N)	Causes of Tx Failure at 24 hours	Tx Failure 72 hours, n (%)	Comorbidities	MV within 72 hours, n (%)	Surfactant Admin. (n/%)	Caffeine (n/%)	Conclusion
Farhat et al. 2018 [29]	NR	NR	NR	NR	IVH: NCPAP:17%, HFNC:16.7% Apnea: NCPAP:17%, HFNC:18.5% Hypercapnia: NCPAP:11.3%, HFNC:13% Sepsis: NCPAP:11.3%, HFNC:5.6% Air leak: NCPAP:9.4%, HFNC:13% Nasal damage: NCPAP:24.5%, HFNC:9.2% PDA: NCPAP:9.4%, HFNC:7.4% BPD: NCPAP:3.8%	NR	NCPAP: 49.1% HFNC: 48.1%	NR	HFNC is a safe method for preterm infants with respiratory distress at birth.
Shin et al., 2017 [30]	NR	NCPAP: 9 (20.9) HFNC: 16 (38.1)	Hypoxia: NCPAP:6 (14.0), HFNC:15 (35.7) Resp. acidosis: NCPAP:4 (9.3), HFNC:2 (4.8)	NR	BPD: HFNC:1 (2.4) Air leak: HFNC:2 (4.8)	NR	Surfactant: NCPAP:7 (16.3), HFNC:12 (28.6)	Caffeine: NCPAP:9 (20.9), HFNC:11 (26.2)	No significant differences in outcomes or complications. HFNC is safe; effectiveness as initial support remains uncertain.
Glackin et al. 2017 [31]	NR	NR	NR	NR	CLD (36/40): NCPAP:68, HFNC:64 Apnea (episodes/day): NCPAP:0.014 (0-0.151)	NR	NR	NR	HFNC did not achieve full oral feeding faster than NCPAP in preterm infants.

ABG, Arterial Blood Gas, BPD, Bronchopulmonary Dysplasia, CLD, Chronic Lung Disease, ELBWI, Extremely Low Birth Weight Infant, FiO_2, Fraction of Inspired Oxygen, HFNC, High-Flow Nasal Cannula, HS-PDA, Hemodynamically Significant Patent Ductus Arteriosus, ICH, Intracerebral Hemorrhage, IVH, Intraventricular Hemorrhage, MV, Mechanical Ventilation, NEC, Necrotizing Enterocolitis, NIV, Non-Invasive Ventilation, NR, Not Reported, NCPAP, Nasal Continuous Positive Airway Pressure, PDA, Patent Ductus Arteriosus, RDS, Respiratory Distress Syndrome, ROP, Retinopathy of Prematurity, SAS, Silverman–Anderson Score, Tx, Treatment, VLBW, Very Low Birth Weight.

Table 4. *RoB: interpretation of the included studies.*

Study	D1	D2	D3	D4	D5	Overall
Grover et al., 2022 [20]	Low	Some concerns	Low	Low	Low	Some concerns
Singh et al., 2022 [21]	Low	Low	Low	Low	Low	Low
Demirel et al., 2021 [22]	Some concerns	High	Low	Some concerns	Low	High
Chen et al., 2020 [23]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Charki et al., 2020 [24]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Akbarian-rad et al., 2020 [25]	Low	Some concerns	Low	Some concerns	Low	Some concerns
Armanian et al., 2019 [26]	Low	Low	Some concerns	Low	Low	Some concerns
Skariah et al., 2019 [27]	High	Some concerns	Low	Low	High	High
Murki et al., 2018 [28]	Some concerns	Some concerns	Low	High	Low	High
Farhat et al., 2018 [29]	Some concerns	Low	Low	Low	Low	Some concerns
Shin et al., 2017 [30]	Low	Low	Some concerns	Some concerns	Low	Some concerns
Glackin et al., 2017 [31]	Low	Low	Low	Some concerns	Low	Some concerns

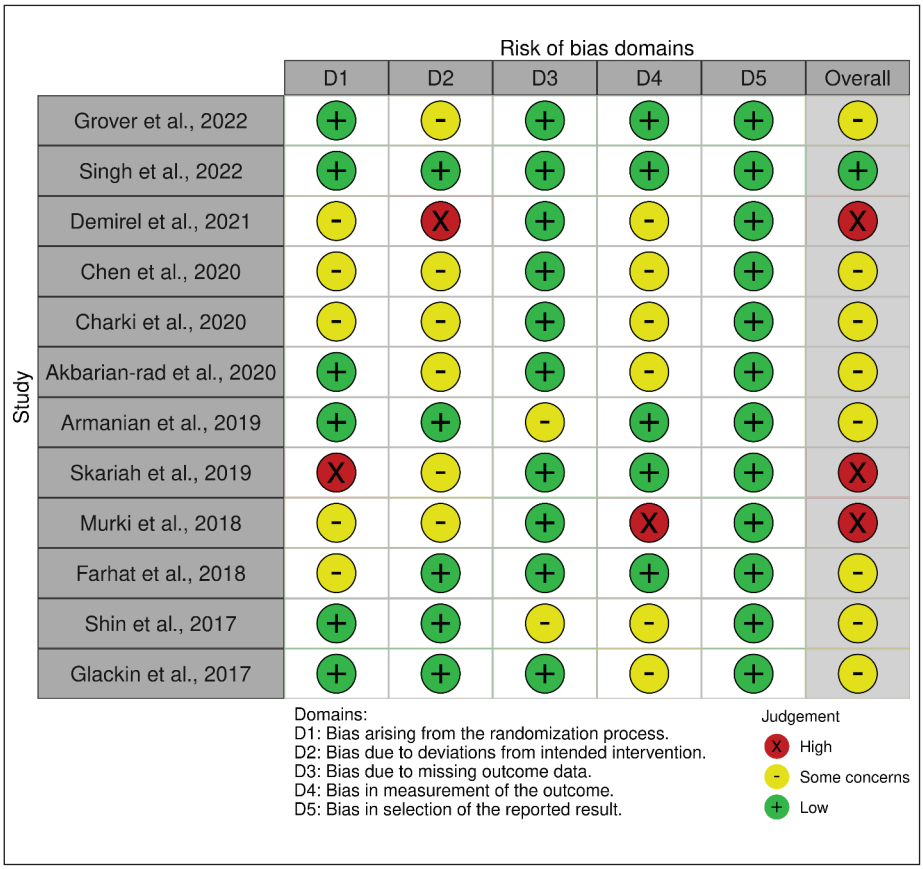

Figure 2*. ROB-2 quality assessment of twelve RCT studies.*

effective alternative to NCPAP, with some advantages in patient comfort and airway safety [20].

In line with several studies reviewed, a comparison of nCPAP and HFNC demonstrated no significant differences in major neonatal outcomes, including mortality, intubation rates, or discharge without ventilation. Interestingly, the HFNC group had shorter durations of non-invasive ventilator support and hospital stay, suggesting potential efficiency benefits. However,

HFNC was associated with more nasal mucosal injury, whereas sepsis was more common in the nCPAP group. Treatment failure was also slightly higher in the HFNC group, indicating that while HFNC is generally safe and effective, clinicians should monitor for specific adverse effects and individualize respiratory support strategies [21,22].

Several of the included studies specifically evaluated the comparative effectiveness of HFNC and NCPAP in preterm infants with respiratory distress, including high-risk neonates and those in the delivery room. A study assessing preterm neonates with gestational ages of 28–36 weeks demonstrated that HFNC provided comparable efficacy and safety to NCPAP for delivery room respiratory support, although the authors noted that noninferiority could not be conclusively established [23]. Similarly, a study focusing on neonates of 32 weeks' gestation reported no significant differences between HFNC and NCPAP in terms of primary respiratory support, time to weaning from the devices, or oxygen requirements during the first hour of life [24,25]. Collectively, these findings reinforce the broader evidence from this review, suggesting that HFNC is generally as safe and effective as NCPAP for moderately preterm infants, while also offering practical advantages such as ease of use and patient comfort.

One trial in infants >28 weeks and >1 kg with RDS found no difference in treatment failure within 7 days post-INSURE, but reported a lower incidence of nasal injury with HFNC, suggesting non-inferiority to NCPAP [26]. Another study in extremely low-birth-weight infants (ELBWI) demonstrated that HFNC was effective in preventing extubation failure, while also reducing oxygen use, nasal trauma, necrotizing enterocolitis, hospital stay, and associated costs [27]. Similarly, a trial evaluating postextubation respiratory support showed comparable primary and secondary outcomes between HFNC and NCPAP, with HFNC again deemed a safe and acceptable alternative. Collectively, these findings support the potential role of HFNC as a non-inferior and better-tolerated modality compared to NCPAP in preterm neonates requiring non-invasive respiratory support [28,29].

One study reported that HFNC was as effective as NCPAP in managing neonates with RDS following surfactant administration, indicating its potential as an alternative support modality [30]. In contrast, another investigation found higher treatment failure rates with HFNC compared to NCPAP and nasal intermittent mandatory ventilation (NIMV), cautioning against its use as first-line therapy [31]. A further study demonstrated that early application of HFNC yielded comparable outcomes to NCPAP as a primary non-invasive respiratory support, although it did not prove superior. Collectively, these findings suggest that while HFNC may be a feasible alternative in selected contexts, its effectiveness relative to established modalities such as NCPAP and NIMV remains inconclusive [32].

Another investigation, comparing HFNC, nCPAP, and NIMV, reported that while HFNC use at birth appeared safe, it was not more effective than the other two approaches in reducing intubation rates. Comparable findings were noted in another study that observed no significant differences between HFNC and NCPAP in terms of respiratory outcomes, complications, or clinical endpoints, though the non-inferiority of HFNC as an initial treatment could not be firmly established. Beyond respiratory endpoints, one study focused on feeding outcomes in preterm infants with evolving chronic lung disease, noting that both HFNC and nCPAP offered comparable support in achieving full oral feeding [33].

However, the evidence for ELBW infants (<1,000 g) and very early preterm neonates is less consistent. Some studies reported higher failure rates, increased need for escalation to invasive support, or slightly better outcomes with NCPAP in this population [34]. These results align with prior research indicating that very fragile neonates may require more aggressive or closely monitored respiratory support. Clinicians should consider gestational age, respiratory effectiveness, and patient tolerance when choosing between HFNC and NCPAP. HFNC may be particularly useful for improving comfort, reducing nasal injury, and facilitating early feeding in preterm infants over 28 weeks' gestation. However, for ELBW infants or those at the highest risk of respiratory failure, NCPAP may still be preferred as the initial respiratory support.

Limitations

This systematic review has several limitations that should be acknowledged. Because the included studies varied widely in design, outcome definitions, and patient populations, meta-analysis was not feasible. We therefore conducted a structured narrative synthesis following PRISMA guidelines. The overall certainty of evidence across the included studies was low to moderate, primarily due to small sample sizes, methodological heterogeneity, and the absence of a formal GRADE assessment. Follow-up in most studies was brief, with long-term outcomes, such as neurodevelopmental status or chronic lung disease, rarely reported. Finally, the generalizability of the findings is limited. Most of the included studies were conducted in high-resource neonatal intensive care units using specific devices, which may not reflect outcomes in lower resource settings or with different equipment. These factors should be considered when interpreting the results of this review.

Conclusion

HFNC is a safe and effective alternative to NCPAP for preterm infants over 28 weeks' gestation, with similar respiratory outcomes and benefits like reduced nasal trauma and lower rates of NEC. HFNC offers ease of use and comfort, particularly in delivery rooms. However, results for ELBW infants and very early preterm neonates have been inconsistent, with some studies showing higher failure rates and increased need for invasive support. While most studies found no significant differences in major outcomes, careful patient selection and monitoring are essential. HFNC can be considered a viable first-line or alternative non-invasive ventilation option, but further multicenter randomized trials are needed to validate its

effectiveness across all gestational ages and improve protocols for ELBW infants.

Conflict of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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Supplementary content (If any) is available online.

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