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COMPARISON OF HIGH-FLOW NASAL CANNULA AND NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE FOR RESPIRATORY SUPPORT IN PRETERM INFANTS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Fadhilah Apriliandri[1*], Danny Yovita Maharani[2], Amelina Ratih Listyaningrum[3]
[1]Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, Indonesia
[2]Faculty of Medicine, Universitas Lampung, Indonesia
[3]Faculty of Medicine, Universitas Yarsi, Indonesia

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Corresponding Author:
E-mail: dhillapr24@gmail.com

ABSTRACT

Background: High-flow nasal cannula (HFNC) has gained increasing use as a non-invasive respiratory support for preterm infants, yet its relative effectiveness and safety compared with continuous positive airway pressure (CPAP) remain uncertain. **Methods:** We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) enrolling preterm infants (<37 weeks gestation) who received either HFNC or CPAP. Comprehensive searches were conducted in PubMed, Cochrane Library, ClinicalTrials.gov, Scopus, and EBSCOhost from 29 May, 2025 to August 17, 2025. The principal outcomes were treatment failure and the requirement for mechanical ventilation. **Results:** Twenty-one RCTs including 2,289 participants met eligibility criteria. Pooled analyses demonstrated no significant differences between HFNC and CPAP in preventing treatment failure (RR 1.18; 95% CI 0.91–1.52) or the need for mechanical ventilation (RR 0.97; 95% CI 0.81–1.16). HFNC was associated with lower rates of nasal trauma, abdominal distension, and pneumothorax. Other endpoints, such as duration of oxygen therapy, time to achieve full enteral feeds, and length of hospitalization, did not differ substantially between the two groups. **Conclusion:** HFNC appears to be as effective as CPAP in preterm infants, with additional advantages in safety and patient comfort. It may therefore represent a reasonable alternative to CPAP, provided that clinical context and individual patient factors are taken into account.

INTRODUCTION

Preterm infants exhibit substantially higher morbidity and mortality rates compared to term infants, largely attributable to their increased susceptibility to respiratory failure.[1,2] Respiratory failure remains one of the leading causes of mortality in neonatal intensive care units (NICUs), emphasizing the critical importance of timely and effective non-invasive respiratory support.[1] Nasal continuous positive airway pressure (CPAP) has historically served as the cornerstone of non-invasive respiratory interventions, with robust evidence demonstrating its ability to reduce respiratory complications, lower mortality rates, and improve long-term neurological outcomes.[3–7] Despite these benefits, CPAP is associated with certain limitations: it requires considerable technical expertise for optimal application, may result in mucosal trauma, septal deformities, granuloma formation, and can cause discomfort due to the fixation devices used.[8,9]

In response to these challenges, high-flow nasal cannula (HFNC), or heated humidified high-flow nasal cannula (HHHFNC), has gained widespread adoption as a potential alternative to CPAP.[10–15] HFNC offers several practical and physiological advantages: it is easier to implement, enhances patient comfort, ensures adequate airway humidification, reduces dead space, and facilitates alveolar recruitment and gas exchange. These characteristics can improve tolerance to prolonged non-invasive respiratory support and

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potentially enhance clinical outcomes in preterm neonates.[10,12,13] However, the comparative effectiveness of HFNC relative to CPAP remains variable across studies. Some randomized trials have reported higher rates of treatment failure with HFNC, particularly among extremely preterm infants, highlighting the need for careful patient selection and protocol standardization.[16]

Previous systematic reviews evaluating HFNC versus CPAP have demonstrated limitations that restrict the generalizability and applicability of their findings. Notably, many reviews were constrained by language restrictions, incomplete reporting of clinically relevant outcomes, and exclusion of recently published randomized controlled trials (RCTs) with larger sample sizes, which could provide more precise estimates of efficacy and safety.[17,18] Given these gaps, an updated meta-analysis that incorporates the most recent and comprehensive evidence is warranted. Such an analysis would not only clarify the relative effectiveness and safety profiles of HFNC and CPAP but also provide clinicians and policymakers with an evidence-based foundation to guide optimal non-invasive respiratory support strategies in preterm infants.

METHODS

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0[19] and was reported according to the PRISMA 2020 statement. The study protocol was prospectively registered in PROSPERO (ID: CRD420251141554).

Literature Search Approach

Comprehensive literature searches were conducted in PubMed, Cochrane Library, ClinicalTrials.gov, Scopus, and EBSCOhost from 29 May, 2025 to August 17, 2025, with no restrictions on language or publication year. The comprehensive search methodology is detailed in the supplementary materials cited at the conclusion of this article.

Inclusion and Exclusion Criteria

Following the PICO framework, eligible studies included preterm infants (born before 37 weeks of gestation) who received high-flow nasal cannula (HFNC) compared to continuous positive airway pressure (CPAP). The primary outcomes assessed were non-invasive respiratory support failure and the requirement for invasive ventilation. Only randomized controlled trials (RCTs) fulfilling these criteria were included. Studies were excluded if they were observational, involved repeat analyses of prior cohorts, were duplicates, or presented incomplete data.

Study Outcomes

The primary outcomes centered on the incidence of failure of non-invasive respiratory support and the requirement for invasive ventilation. Secondary outcomes included complications such as pneumothorax, nasal trauma, abdominal distension, bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), in addition to surfactant administration, mortality, duration of oxygen treatment, length of hospital stay, and time to achieve full enteral feeding.

Selection Process and Bias Assessment

Two independent reviewers conducted screenings of the titles, abstracts, and full manuscripts. The risk of bias in the included trials was assessed using the Cochrane RoB 2 tool, which encompasses five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Each domain was evaluated using specific guiding questions, including the assessment of sequence generation and allocation concealment for randomization. Discrepancies were resolved through discussion or by consulting a third reviewer.

Information Extraction

Data were independently extracted by two reviewers using a standardized data collection form. Extracted information included study details (author, publication year, country), participant demographics (gestational age, sample size), intervention specifics (HFNC flow rates, CPAP pressures), and clinical outcomes of interest. When data were unclear or missing, the original study authors were contacted for clarification.

Statistical Analysis

Data were analyzed using Review Manager version 5.4 (Cochrane Collaboration, Copenhagen,

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Denmark). Dichotomous variables were summarized as relative risks (RR) with 95% confidence intervals (CI), while continuous outcomes were presented as weighted mean differences (WMD) with 95% CI. When only medians and interquartile ranges were available, means and standard deviations were derived using the method described by Wan et al.[39] Statistical significance was defined as $p \leq 0.05$. The heterogeneity among studies was evaluated through the χ^2 test and quantified using the I^2 statistic. A fixed-effects model was utilized when heterogeneity was minimal ($I^2 \leq 50\%$), while random-effects modelling was employed for substantial heterogeneity ($I^2 > 50\%$ or $p < 0.1$). Sensitivity analyses were conducted by excluding studies that may have contributed to heterogeneity. Subgroup analyses were performed when possible, such as based on gestational age or clinical indication. Funnel plot visualization was utilized to assess publication bias when the number of included studies surpassed ten.

RESULTS

Overview of Included Studies

The literature search initially identified 1,145 records. Following title/abstract screening and full-text assessment, 21 randomized controlled trials met the eligibility criteria and were included in the final analysis, comprising a total of 2,289 preterm infants (1,134 allocated to HFNC and 1,155 to CPAP). The study selection process is outlined in Figure 1 (PRISMA flow diagram).

Preterm infants were defined according to the World Health Organization (WHO) standard as those born before 37 completed weeks of gestation. Across the included trials, the gestational age of enrolled infants ranged from <28 weeks to 36 weeks, reflecting variability in population characteristics across studies[43]. Intervention parameters also varied, with HFNC flow rates reported between 1 and 8 L/min, while CPAP pressures ranged from 3 to 8 cmH_2O. An overview of the key study characteristics, including sample size, country, gestational age, birth weight, intervention details, and outcomes assessed, is presented in Table 1.

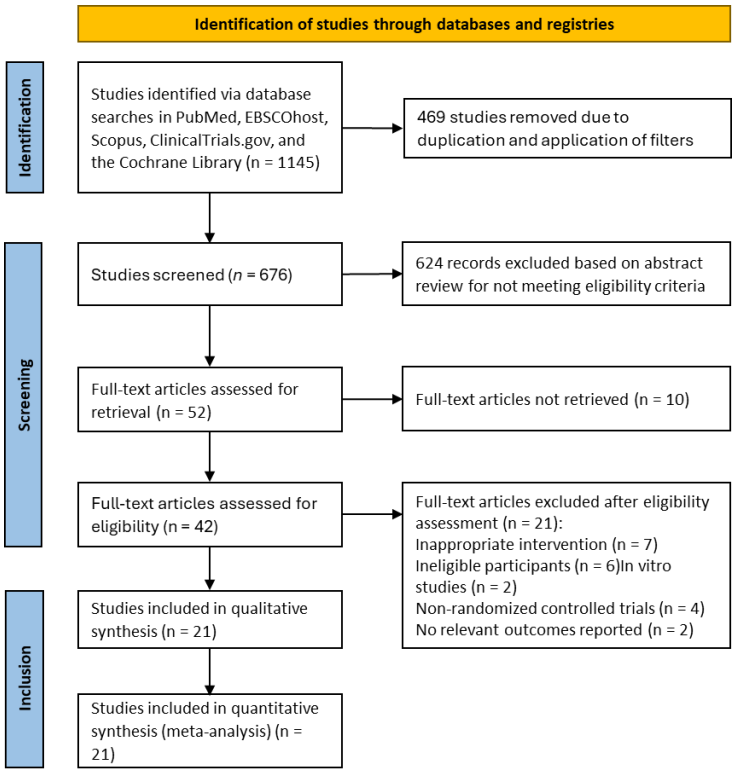

Figure 1. PRISMA flow diagram

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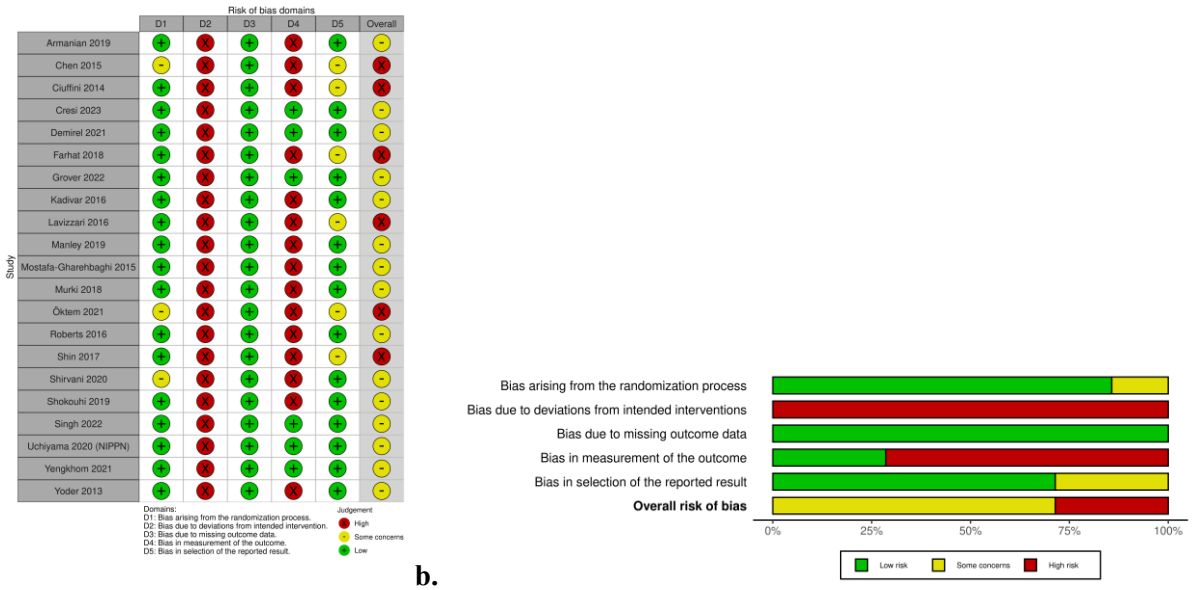
Table 1. Summary of Randomized Controlled Trials (RCTs) Comparing High-Flow Nasal Cannula (HFNC) and Continuous Positive Airway Pressure (CPAP) in Preterm Neonates

AUTHOR	YEAR PUBLICATION	COUNTRY	GESTATIONAL AGE	N (HFNC/CPAP)	HFNC (FLOW RATE)	CPAP (PRESSURE)
Armanian[20]	2019	Iran	<37 weeks	35 / 37	2,5–3 L/min	5–6 cmH_2O
Chen[21]	2015	China	<37 weeks	34 / 32	2–8 L/ min	5–7 cmH_2O
Ciuffini[22]	2013	Italy	29–36 weeks	85 / 92	4–6 L/ min	4–6 cmH_2O
Cresi[23]	2023	Italy	25–29 weeks	125 / 122	4–7 L/ min	5–7 cmH_2O
Demirel[24]	2019	Turkey	<32 weeks	53 / 54	6–8 L/ min	6–7 cmH_2O
Farhat[25]	2018	Iran	28–34 weeks	54 / 53	2–5 L/ min	6–8 cmH_2O
Grover[26]	2022	India	28–36 weeks	61 / 63	4–8 L/ min	5–8 cmH_2O
Kadivar[27]	2016	Iran	28–34 weeks	27 / 27	2–4 L/ min	5–8 cmH_2O
Lavizzari[11]	2016	Italy	29–36 weeks	158 / 158	4–6 L/ min	4–6 cmH_2O
Manley[4]	2019	Australia	31–34 weeks	72 / 68	6–8 L/ min	6–8 cmH_2O
Mostafa[28]	2015	Iran	30–34 weeks	42 / 43	6 L/ min	5–6 cmH_2O
Murki[29]	2018	India	28–37 weeks	133 / 139	5–7 L/ min	5–7 cmH_2O
Öktem[30]	2021	Turkey	<32 weeks	20 / 20	5 L/ min	5–6 cmH_2O
Roberts[31]	2016	Australia & Norwegia	28–37 weeks	278 / 286	6–8 L/ min	6–8 cmH_2O
Shin[32]	2017	Korea	30–35 weeks	42 / 43	3–7 L/ min	4–7 cmH_2O
Shirvani[33]	2020	Iran	<34 weeks	30 / 30	3–7 L/ min	4–6 cmH_2O
Shokouhi[34]	2019	Iran	28–36 weeks	30 / 30	2–8 L/ min	4–8 cmH_2O
Singh[35]	2022	India	28-32 weeks	15 / 15	2–8 L/ min	5–7 cmH_2O
Uchiyama[36]	2020	Japan	<34 weeks	176 / 196	≤8 L/ min	4–5 cmH_2O**
Yengkhom[37]	2020	India	28–36 weeks	63 / 65	4–7 L/ min	5–7 cmH_2O
Yoder[38]	2013	United States	28–32 weeks	75 / 75	2–8 L/ min	5–8 cmH_2O

Evaluation of Study Bias

All included studies were randomized controlled trials. According to the RoB 2 assessment, most studies exhibited low risk for randomization and data completeness, but some concerns persisted regarding deviations from intended interventions and challenges in outcome assessment, mainly due to lack of blinding. Overall, the risk of bias ranged from "some concerns" to "high risk" (see Figures 2–3).



a. **b.**

Figure 2. *Risk of bias assessment using the Cochrane RoB 2 tool: (a) individual risk of bias assessment for each included study; (b) overall summary of risk of bias across all studies.*

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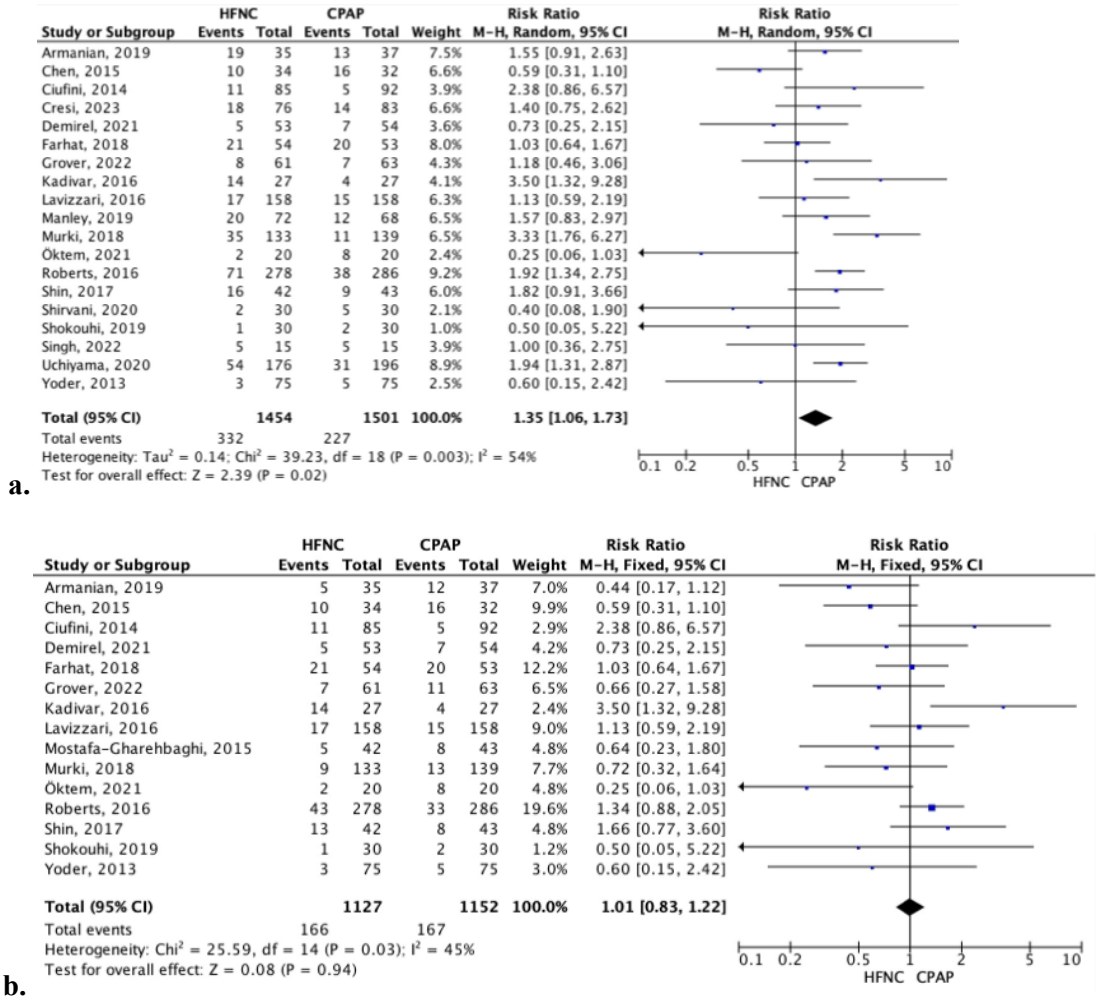

Figures 3. *Forest plots for non-invasive respiratory support failure (a) and mechanical ventilation requirement (b).*

Primary Outcomes

Seventeen studies reported outcomes related to failure of non-invasive respiratory support. The pooled analysis indicated no significant difference between HFNC and CPAP (RR 1.18; 95% CI 0.91–1.52; p = 0.21; I^2 = 55%) (Figure 4). Similarly, across 15 studies assessing the requirement for mechanical ventilation, no statistically significant difference was observed between the two groups (RR 0.97; 95% CI 0.81–1.16; p = 0.73; I^2 = 42%).

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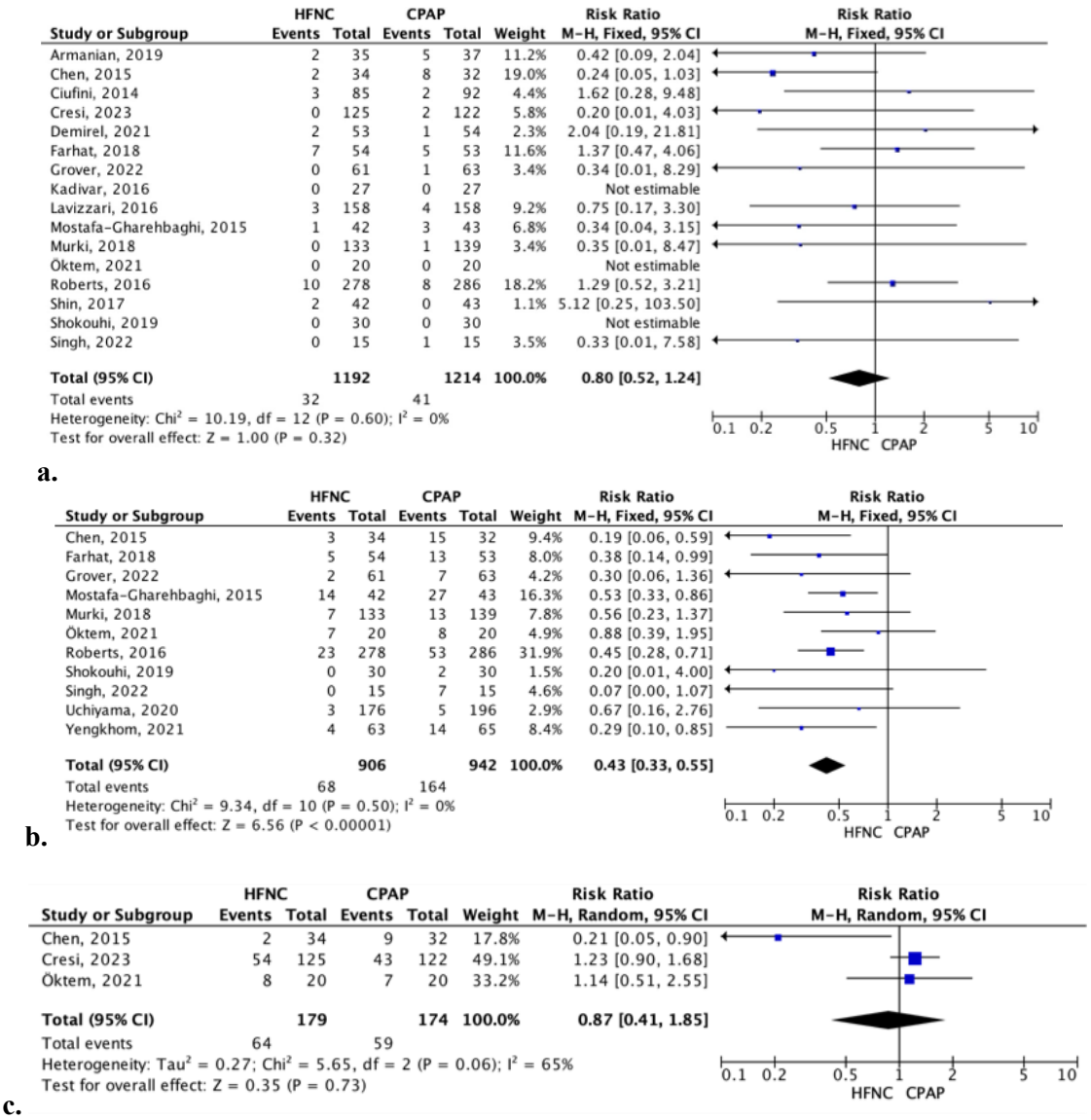

Figures 4. *Forest plots for safety outcomes: a) pneumothorax, b) nasal trauma, c) abdominal distension.*

Secondary Outcomes

a. Safety

Use of HFNC was linked to a lower risk of certain complications compared with CPAP. Specifically, pneumothorax occurred less frequently in the HFNC group (RR 0.62; 95% CI 0.44–0.88; p = 0.007; I^2 = 0%) (Figure 6a). The risk of nasal trauma was also reduced (RR 0.36; 95% CI 0.28–0.46; p < 0.00001; I^2 = 5%) (Figure 6b), as well as abdominal distension (RR 0.47; 95% CI 0.26–0.85; p = 0.01; I^2 = 61%) (Figure 6c). For other safety parameters, such as surfactant administration, bronchopulmonary dysplasia, sepsis, NEC, IVH, PDA, ROP, and mortality, no significant group differences were found.

b. Clinical Outcomes

For clinical outcomes, the results were generally consistent. No significant differences emerged between groups in terms of age at initiation of enteral feeding (MD –1.45 days; 95% CI –3.92 to 1.02; p = 0.25; I^2 = 93%), duration of hospital stay (MD –0.22 days; 95% CI –1.39 to 0.96; p = 0.71; I^2 = 11%), length of non-invasive respiratory support, or total

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duration of oxygen therapy (MD –1.10 days; 95% CI –3.12 to 0.92; p = 0.29; I^2 = 92%.

Sensitivity Analysis and Publication Bias

For non-invasive respiratory support failure, initial heterogeneity was moderate (I^2 = 54%; p = 0.02). After excluding the study by Chen et al.[21], heterogeneity decreased to 44% and results became more consistent (p = 0.001). For mechanical ventilation, initial heterogeneity was 45% (p = 0.94) and decreased to 31% after excluding the study by Kadivar et al., with no change in significance (p = 0.59). For abdominal distension, high initial heterogeneity (I^2 = 65%; p = 0.73) dropped to 0% after excluding Chen et al.[21], but results remained non-significant (p = 0.19). These findings suggest that the main conclusions are relatively robust to variations among included studies.

Publication bias was assessed using funnel plots. For primary outcomes (respiratory support failure and mechanical ventilation), the distribution appeared symmetrical, indicating a low risk of publication bias.

DISCUSSION

This meta-analysis indicates that high-flow nasal cannula (HFNC) demonstrates efficacy comparable to nasal continuous positive airway pressure (CPAP) in preterm infants, both in preventing failure of non-invasive respiratory support and in reducing the necessity for mechanical ventilation. Moreover, HFNC consistently reduced the incidence of pneumothorax, nasal trauma, and abdominal distension, highlighting a favourable safety profile. These results suggest that HFNC represents a viable alternative to CPAP, particularly in clinical scenarios where patient comfort and airway protection are prioritized.

The findings of this study align with previous research by Hong et al.[17] and Luo et al.[18], which also reported no statistically significant differences in efficacy between HFNC and CPAP. Similarly, the Cochrane meta-analysis by Wilkinson et al.[13] and the systematic review by Lavizzari et al.[11] support the use of HFNC as an appropriate non-invasive respiratory support modality for preterm infants. Our meta-analysis adds further value by incorporating the most.

Recent randomized controlled trials (RCTs) with larger sample sizes and by evaluating additional clinically relevant outcomes, including length of hospital stay and time to achieve full enteral feeding. Consequently, this study provides a more comprehensive and updated synthesis of evidence compared to prior reviews.[17,18,40]

Nevertheless, heterogeneity among included studies warrants careful consideration. Variations in study protocols—such as gestational age ranges, HFNC flow rates (1–8 L/min), and CPAP pressures (3–8 cmH_2O)—likely contributed to differences in clinical outcomes. Large-scale RCTs, such as those conducted by Roberts et al.[31] and Murki et al.[29], employed intervention parameters that differed from other studies. Specifically, Roberts et al.[31] applied relatively high HFNC flow rates (6–8 L/min) in extremely preterm infants as initial respiratory support, whereas Murki et al.[29] used lower flow rates (2–4 L/min) in infants with more advanced gestational ages. These discrepancies in population characteristics and intervention protocols may partially explain inter-study heterogeneity and can affect the consistency of pooled results.

Sensitivity analyses confirmed that, although heterogeneity decreased after excluding certain studies (Chen et al.[21] and Kadivar et al.[27]), the direction of the effect remained consistent. This indicates that the primary conclusions are robust and not unduly influenced by individual studies. An important clinical consideration is the use of HFNC in extremely preterm infants (<28 weeks gestation). Landmark trials by Finer et al.[6] and Dunn et al.[5] emphasize the benefits of early CPAP in this vulnerable population, while individual RCTs[32,33,41] report relatively higher failure rates with HFNC. This observation is consistent with the systematic review by Schmölzer et al.[7], which recommends CPAP as the primary modality for infants born before 28 weeks gestation. Accordingly, CPAP should remain the first-line intervention in extremely preterm neonates, whereas HFNC may be suitable for more mature preterm infants or as sequential therapy following CPAP.

From a physiological standpoint, HFNC offers several advantages, including improved patient comfort, reduction in dead space, and optimal humidification of the airway, which collectively may enhance respiratory efficiency, maintain stable inspiratory temperature and humidity, and improve tolerance during prolonged therapy.[1,4]In contrast, CPAP provides a more consistent positive alveolar

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pressure, thereby maintaining lung recruitment, particularly in extremely preterm infants with low pulmonary compliance.[1,4,42] This difference may explain why CPAP retains certain advantages in specific subpopulations.

Clinically, these findings support the use of HFNC as an alternative or sequential therapy after CPAP, particularly for infants with higher gestational ages, where it may reduce the risk of nasal trauma and other complications. Nevertheless, in extremely preterm infants, CPAP should continue as the primary support modality, with HFNC applied selectively based on individual patient condition and NICU resources.

This study has several limitations. First, variability in protocols across studies could have influenced outcome measures. Second, risk of bias persisted in blinding domains, which is a common limitation in non-invasive neonatal trials. Third, although funnel plots were employed to evaluate publication bias, formal statistical tests such as Egger's test were not performed. Fourth, subgroup analyses could not be undertaken due to insufficient data, limiting the interpretability of results in extremely preterm populations. Fifth, despite protocol registration, the majority of included RCTs were of moderate quality with considerable variability in study design. These limitations align with those described in the Cochrane Handbook[19] and should be considered when interpreting the results.

Overall, this meta-analysis provides strong evidence supporting HFNC as a safe and effective alternative to CPAP in preterm infants. Nonetheless, its use in extremely preterm neonates requires caution, and CPAP remains the recommended modality for this high-risk population.

CONCLUSIONS

This meta-analysis demonstrates that HFNC has comparable efficacy to CPAP in preterm infants for preventing non-invasive respiratory support failure and the need for mechanical ventilation. HFNC also offers safety advantages, notably reducing the risk of nasal trauma, pneumothorax, and abdominal distension. However, CPAP remains more consistent in preventing post-extubation failure. Therefore, HFNC can be considered a viable alternative to CPAP in clinical practice, with the choice of modality tailored to patient condition, available resources, and clinician experience.

ETHICAL APPROVAL

There is no ethical approval.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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