Use of NHFOV versus NIPPV for the respiratory support of preterm newborns: a meta-analysis

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Abstract

Background: Noninvasive ventilation for newborns has become the preferred mode of treatment for respiratory diseases. **Objectives:** This meta-analysis evaluated and compared the efficacy and safety of noninvasive high-frequency oscillatory ventilation (NHFOV) and nasal intermittent positive-pressure ventilation (NIPPV) for use with newborns. **Study design:** We searched the PubMed, Cochrane Library, EMBASE, Web of Science,CNKI, Wanfang and VIP databases from inception to April 1, 2022. Randomized controlled trials (RCTs) and cohort studies that evaluated and compared the effectiveness of NHFOV and NIPPV in newborns were included in the review and meta-analysis, which followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. **Results:** Twenty-three articles involving 2,924 patients were included. Compared to NIPPV, NHFOV showed a significantly greater reduction in the intubation rates in initial respiratory support and in the reintubation rate without time limit. While reintubation rates within 72 h and 7 days of post-extubation respiratory support were similar. Significant decreases in the duration of non-invasive ventilation and length of hospital stay were observed with NHOFV, which also: reduced PaCO2 levels, enhanced PaO2 levels and the SpO2/FiO2 ratio at 1 h and 24 h after non-invasive respiratory support; and significantly reduced the risk of bronchopulmonary dysplasia and apnea. **Conclusions:** Compared to NIPPV, NHFOV is a safer and more effective neonatal respiratory support modality. The potential benefits of NHFOV as a mode of respiratory support for very low birth weight or extremely preterm infants should be investigated in larger trials.

Introduction

Preterm infants are prone to various conditions because of their immature organs. Respiratory failure related to organ immaturity is the most common cause of death in preterm infants. Invasive mechanical ventilation (IMV), which has been widely used in past decades to support neonates with respiratory failure, has many complications (air-leaks, ventilator-associated lung injury and bronchopulmonary dysplasia (BPD)) (1). Life-saving strategies that minimize injury to the lung and other organ systems, thereby reducing long-term morbidity, have been the focus of recent attention.

Given the emergence of noninvasive nasal airway interfaces for newborns, noninvasive ventilation has become a suitable technique for the treatment of neonatal respiratory diseases. The American Academy of Pediatrics and European Consensus Guidelines recommend early non-invasive ventilation for the treatment of respiratory diseases in preterm infants, citing its promising curative effects (2, 3). Noninvasive intermittent positive pressure ventilation (NIPPV) superimposes an intermittent peak pressure on continuous positive airway pressure (CPAP). The popularity of NIPPV has risen since its recent comparison to nasal CPAP, in which NIPPV significantly decreased the rates of respiratory failure, reintubation and the need for a

ventilator (4). Synchronized NIPPV is the best respiratory support modality post-extubation (5), although synchronization is difficult to achieve and often unavailable. A more recent alternative is noninvasive high frequency oscillatory ventilation (NHFOV), which has the characteristics of high frequency ventilation and nasal CPAP, and does not need synchronization; it also has the advantages of being noninvasive, highly efficient in CO2 removal and has a lower volume/barotrauma (6). Compared with NIPPV and a nasal CPAP, NHFOV can reduce the need for IMV in infants treated for respiratory distress syndrome (RDS) (7). However, some RCTs have not reported a reduced intubation rate, a shortened time for oxygen therapy or non-invasive ventilator-assisted ventilation when using NHFOV versus NIPPV (8, 9). Given these conflicting findings, we conducted a comprehensive systematic review and meta-analysis to evaluate relevant evidence from published studies.

Methods

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10).

Search strategy

Two authors independently searched the PubMed, Cochrane Library, EMBASE, Web of Science,CNKI, Wanfang and VIP databases from inception to April 1, 2022. We used the following search terms: ((Infant OR newborn OR neonat* OR premature OR very low birth weight OR low birth weight OR VLBW OR LBW) AND (Noninvasive High-Frequency Oscillatory Ventilation OR Noninvasive High Frequency Oscillation Ventilation OR Non-invasive high-frequency oscillatory ventilation OR NHFOV OR nHFV) AND (nasal intermittent positive pressure ventilation OR NIPPV OR nasal intermittent mandatory ventilation OR NIMV OR non-invasive positive pressure ventilation OR synchronized intermittent mandatory ventilation OR nasopharyngeal synchronized intermittent mandatory ventilation)). No language restrictions were applied. A third author was consulted for authors' differences in opinion during the study selection process.

Inclusion and exclusion criteria

All included studies met the following criteria: (1) randomized controlled trial (RCT) or cohort study; (2) the intervention group was given NHFOV and the comparison group was given NIPPV as initial respiratory support or post-extubation respiratory support; and (3) at least one of the following outcome parameters was reported. The primary outcome was the rate of intubation or reintubation, indicating the need for IMV after non-invasive respiratory support or extubation. The secondary outcomes included: (i) the duration of non-invasive ventilation, (ii) total oxygen therapy time, (iii) length of hospital stay (LOS) , (iv) blood gas analysis indices (PaO2 and PaCO2 levels and SpO2/FiO2 ratios) 1 h and 24 h after non-invasive respiratory support and (v) adverse outcomes, including air leak, abdominal distension, BPD, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), nasal injury, periventricular leukomalacia, pneumothorax (PNX) and apnea.

The exclusion criteria were: (1) non-clinical studies, (2) research protocols, (3) duplicated reports or secondary or post-hoc analyses of the same study population or (4) lack of sufficient information related to baseline or outcome data.

Data extraction

Two authors used pre-designed tables to extract data independently from each of the eligible studies. Disagreements between the two investigators were resolved by discussion or consensus with a third author. We extracted the characteristics of each study and recorded the following data: first author, year of publication, study design, characteristics of the study population, sample size and details related to the methodological quality and results. The numeric results, statistics used and p values were extracted for each outcome. We attempted to contact the author of the original report to obtain further details when the any of the above information was unclear.

Quality assessment and publication bias

We assessed the quality of the included trials based on the information in the Methods section and supplementary materials about them. The quality of the RCTs was assessed using the Cochrane Collaboration's risk-of-bias tool for randomized trials (RoB) (11), which consists of six domains and allowance for any other bias, with risk-of-bias judgements for RCTs ranging from "high," "unclear" to "low." We assessed observational studies using the Newcastle-Ottawa Scale (12) with scores ranging from 0 to 9 points (a higher score indicated less bias). Two authors independently assessed the studies' quality and resolved disagreements through consensus.

We used funnel plots to assess publication bias, which were calculated using RevMan 5.3 software. The Egger regression test was used to measure funnel plot asymmetry, and was calculated using Stata 12.0 (StataCorp LP, College Station TX, USA).

Data synthesis and analysis

Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to calculate the pooled estimates. Odds ratios (OR) for dichotomous outcomes, the standardized mean difference (SMD) for continuous data and corresponding 95% confidence intervals (CI) were used for the analyses. The I^2 statistic was used to evaluate the effect of heterogeneity on the pooled results ($I^2 > 50\%$ indicated substantial heterogeneity). A fixed-effects model was used to pool data when the heterogeneity was not significant and a random effects model was used when significant heterogeneity was identified. We performed sensitivity analyses of all outcome parameters by adjusting the effects of the models to assess the robustness of the results. We perfomed subgroup analyses by type of study and initial or post-extubation respiratory support. A p -value < 0.05 was considered statistically significant.

Results

Study inclusion and characteristics

In the initial literature search (up to 1, April 2022), 323 records were yielded. After removing duplicates, we screened the titles and abstracts of 299 records and excluded 260 that did not meet our eligibility criteria. After evaluating the full text of the remaining 39 records, we included 21 in our meta-analysis (7-9, 13-30). In an additional literature search (performed just before the article's submission), we identified one additional eligible article (36). Finally, 22 articles were included in our study (Fig. 1).

We regarded the Yuan et al. study as two trials because it reported separate analyses of two different age groups (14). Therefore, we included 23 trials (15 RCTs and eight cohort studies) consisting of 2,924 participants, of whom 1,451 received NHFOV for respiratory support. Eleven trials compared NHFOV and NIPPV for initial respiratory support of neonates (7, 13-15, 18, 23-25, 27, 29), and 12 trials compared NHFOV and NIPPV for respiratory support after extubation (8, 9, 16, 17, 1-22, 26, 28, 30, 36); 14 trials concentrated on premature infants with RDS (7, 8, 13-15, 17-20, 22, 23, 28-30); four concentrated on neonates with respiratory failure; 1 focused on severe BPD (9) and 1 concentrated on meconium aspiration syndrome (18). The remaining 3 trials did not limit specific disease types (16, 21, 36) (Table 1).

Methodological quality and risk of bias

The quality of the cohort studies was characterized as good, as measured by the Newcastle-Ottawa scale, with most studies scoring [?] 7 out of 9 points (Table 1). The RCTs were assessed using the Cochrane Collaboration risk of bias (RoB) tool (11). Although all included RCTs conducted randomization, five of them did not adequately describe their randomization methods. Only two studies used sequentially numbered sealed opaque envelopes for allocation, 1 used a third party for allocation, 1 used software-generated random number sequence for allocation and the others never mentioned an allocation scheme. Eleven studies had an unclear risk of bias due to performance and detection bias. The infants and personnel could not be blinded due to the nature of intervention and three studies were judged to have a high risk of bias due to performance bias; however, the outcome assessor was blinded, resulting in a low risk of bias due to detection bias (suppl. eFig. 1, eFig. 2).

Primary outcome

Seven trials (7, 13-15, 18, 29) that reported intubation rates indicated that NHFOV reduced the intubation rate significantly, compared with NIPPV (Fig. 2). However, the subgroup analysis by study type found no significant differences in the rates between NHFOV and NIPPV in the cohort studies or RCTs (Fig. 2).

Three trials (8, 26,36) did not limit the time of reintubation, and indicated that NHFOV reduced the reintubation rate significantly, compared with NIPPV (Fig. 3a). However, the subgroup analysis by study type found no significant differences in the rates between NHFOV and NIPPV in the cohort studies or RCTs (Fig. 3a). Five RCTs (8, 9, 17, 20, 28) reported reintubation rates within 72 h. No significant difference was found in the reduction of the reintubation rate between NHFOV and NIPPV (Fig. 3b). Four trials (16, 19, 21, 22) that reported reintubation rates within 7 days found no significant differences between NHFOV and NIPPV(suppl. eFig. 3). Stratification of the results by study design showed the pooled random effects OR was 0.70 for RCTs and 0.72 for cohort studies (suppl. eFig. 3).

Secondary outcomes

Fourteen studies (8, 13-19, 22, 24, 26, 28, 36) that enrolled 2,083 neonates reported the duration of non-invasive ventilation, and found a significant decrease in the duration of non-invasive ventilation using NHFOV (standard mean difference (SMD) = -0.98, 95%CI -1.52, -0.45, I2 = 96%, p = 0.0003; suppl. eFig. 4). The subgroup analysis showed a significant difference in post-extubation respiratory support in the cohort studies and RCTs (SMD = -0.47, 95%CI -0.84, -0.09, I2 = 0%, p = 0.01; SMD = -1.52, 95%CI -2.58.-0.45, I2 = 98%, p = 0.005), whereas no significant differences were observed in initial respiratory support (SMD = -0.15, 95%CI -0.49, 0.19, I2 = 41%, p = 0.40) (SMD = -1.20, 95%CI -2.88, 0.48, I2 = 97%, p = 0.16).

Ten studies (9, 14, 16-18, 24, 26, 28, 36) with 1,792 neonates that reported the total oxygen therapy time found no significant differences between the NHFOV and NIPPV groups (SMD = -0.08, 95%CI -0.28, 0.12, I2 = 69%, p = 0.45; suppl. eFig. 5). No significant differences were found in the subgroup analysis of two cohort studies and two RCTs in the total oxygen therapy time in the initial respiratory support (SMD = -0.23, 95%CI -0.71, 0.25, I2 = 67%, p = 0.34) (SMD = -0.11, 95%CI -0.42, 0.20, I2 = 0%, p = 0.47). Nor were significant differences found among the pooled data of five RCTs post-extubation respiratory support between NHFOV and NIPPV (SMD = -0.01, 95%CI -0.37, 0.35, I2 = 84%, p = 0.95).

Nine studies (7, 9, 14, 16, 18, 24, 26, 27) with 948 neonates that reported LOS showed a significant difference in the decreased LOS (SMD = -0.24, 95%CI -0.47, -0.01, I^2 = 66%, p = 0.04; suppl. eFig. 6). The subgroup analysis showed no significant difference in the initial respiratory support of the pooled data between the cohort study and RCTs (SMD = -0.26, 95%CI -0.72, 0.19, I^2 = 84%, p = 0.26; SMD = -0.06, 95%CI -0.37, 0.25, I^2 = 0%, p = 0.69).

Three trials (24, 25, 27) with 291 neonates reported the results of blood gas analyses (PaO2 and PaCO2 levels and SpO2/FiO2 ratios) 1 h after initial non-invasive respiratory support. The NHFOV significantly reduced PaCO2 levels (SMD = -1.48, 95%CI -1.74, -1.22, I^2 = 0%, p <0.001) and increased PaO2 levels (SMD = 0.42, 95%CI 0.19, 0.65, I^2 = 0%, p< 0.001) and the SpO2/FiO2 ratio (SMD = 0.47, 95%CI 0.24, 0.70, I^2 = 0%, p < 0.001) in neonates, unlike NIPPV (suppl. eTable 1).

Seven trials (14, 15, 17, 18, 20, 29) enrolling 540 neonates reported PaCO2 levels 24 h after non-invasive respiratory support. According to the meta-analysis, NHFOV (but not NIPPY) reduced PaCO2 levels significantly (SMD = -0.64, 95%CI -0.92, -0.36, I^2 = 60%, p <0.001) in neonates. Six trials (14, 15, 17, 18, 29) reported PaO2 levels and the meta-analysis indicated that NHFOV significantly enhanced PaO2 levels (SMD = 0.40, 95%CI 0.14, 0.67, I^2 = 55%, p = 0.003) compared with NIPPV. Significant differences were found only in the pooled data of RCTs of initial respiratory support (SMD = 0.57, 95%CI 0.26, 0.88, I^2 = 45%, p < 0.001. Five trials (14, 15, 18, 29) that reported SpO2/FiO2 ratios, found that NHFOV significantly enhanced the SpO2/FiO2 ratio (SMD = 0.56, 95%CI 0.29, 0.83, I^2 = 29%, p <0.001). The subgroup analysis showed a significant difference only in the pooled RCT data for initial respiratory support (SMD = 0.42, 95%CI 0.07, 0.76, I^2 = 66%, p = 0.02;suppl. eTable 1).

Seventeen studies (13-17, 19, 22-24, 26-29, 36) with 2,491 neonates reported adverse outcomes, including the incidence of BPD, and showed that NHFOV reduced the risk of BPD (OR = 0.77, 95%CI 0.63, 0.94, I2 = 0%, p = 0.01; suppl. eTable 2). In the subgroup analysis, significant differences were observed in the meta-analyses of RCTs for initial respiratory support (OR = 0.49, 95% CI 0.25, 0.94, I2 = %, p = 0.03).

Seven studies (14, 17, 23, 24, 27, 28) with 674 neonates reported the incidence of apnea, and showed that the NHFOV resulted in a significant reduction in apnea (OR = 0.55, 95%CI 0.34, 0.88, $I^2 = 0\%$, $p = 0.01$;suppl. eTable 2). However, no significant differences were found between NHFOV and NIPPV after a subgroup analysis by study type and initial or post-extubation respiratory support.

Furthermore, NHFOV reduced the incidence of abdominal distention in post-extubation respiratory support in cohort studies (OR = 0.22, 95%CI 0.07, 0.71, $I^2 = 0\%$, $p = 0.01$; suppl. eTable 2). No significant differences in the likelihood of other adverse outcomes (including air leaks, NEC, IVH, nasal injury, ROP, PNX and periventricular leukomalacia) were observed (suppl. eTable 2).

Publication bias

We evaluated publication bias among the outcome parameters of abdominal distention, NEC, BPD, nasal injury, total oxygen therapy time and the duration of non-invasive ventilation, which was referenced in more than 10 articles. The results suggested that the abdominal distention, nasal injury, total oxygen therapy time and BPD funnel plots we assessed were symmetrical, and the results of Egger's test were not significant, indicating the absence of publication bias. However, the NEC and duration of the non-invasive ventilation funnel plots were asymmetrical, and Egger's test showed a significant difference, indicating publication bias (suppl. eFigs. 7a, 7b, 7c, 7d, 7e, 7f).

Sensitivity analysis

The outcome of reintubation rate without time limit and within 72 h changed when we applied different models to the sensitivity analyses, suggesting that the results were not robust and should be interpreted with caution (Table 2).

Discussion

This meta-analysis of 23 trials with 2,924 participants compared the respiratory support for neonates using NHFOV and NIPPV. The results showed that compared with NIPPV, NHFOV reduced the intubation rate in the initial respiratory support and the reintubation rate without time limit in the post-extubation respiratory support. While the rate of reintubation within 7days and 72h were similar. NHFOV decreased the duration of non-invasive ventilation, in post-extubation respiratory support, and no difference between the two ventilation modes was observed in the initial respiratory support. Newborns' LOS was also decreased with NHFOV, although a significant difference was found only in post-extubation respiratory support in premature infants with respiratory failure (28–34 weeks of gestation, $<$ 2,000 g birth weight) (26). Finally, NHOFV reduced PaCO2 levels and enhanced PaO2 levels and the SpO2/FiO2 ratio at 1 h and 24 h after non-invasive respiratory support. The risk of BPD, apnea and abdominal distention was reduced by NHFOV, but not NIPPV. However, the results should be interpreted with caution because of the significant heterogeneity among the included studies, the high sensitivity observed in the analysis of the reintubation rate without time limit and within 72 h, and the asymmetric funnel plot of the duration of non-invasive ventilation and the NEC incidence.

Complications caused by IMV seriously affect the long-term quality of life of newborns and increase an already large burden on their families. Avoidance of endotracheal intubation and IMV has become a goal of neonatal physicians. We found that NHFOV significantly reduced intubation rates during initial respiratory support, unlike NIPPV. This difference can be explained partly by the ability of NHFOV to improve alveolar ventilation and promote carbon dioxide excretion (31). The superiority of NHFOV over NIPPV, in terms of CO2 clearance efficacy has been demonstrated. After 1 h and 24 h of non-invasive respiratory support, NHOFV significantly reduced PaCO2 levels unlike NIPPV. However, the reintubation rate in post-extubation respiratory support should be viewed with caution. Our study showed that NHFOV reduced the

reintubation rate without time limit, but this was not robust in the sensitivity analysis. Efficacious clearance of PaCO2 is only one of several factors that might help prevent extubation failure. The pre-extubation mean airway pressure (MAP), FiO2 and tidal volume also influenced the success of extubation. Unfortunately, the mechanical ventilation parameters before extubation were not detailed in the included studies. In very low-birth weight preterm infants (< 1,500 g), NHFOV influenced post-extubation respiratory support. The study by Z. Wang et al. (28) of preterm very low birthweight infants treated with NHFOV versus NIPPV reported that NHFOV reduced the reintubation rate within 72 h of extubation. The Y. Li et al. study of preterm infants (16) also found that NHFOV had a lower reintubation rate within 7 days of extubation, unlike NCPAP and NIPPV. Unfortunately, we did not conduct a subgroup analysis based on gestational age or birth weight, which is one of the study's limitations.

In terms of adverse outcomes, NHFOV significantly reduced the risk of BPD, compared with NIPPV. Attenuation of intra-tracheal pressure with NHFOV lowered alveolar pressure, thereby maintaining the end-expiratory volume at a normal level without atelectatic trauma to the lung parenchyma, thus reducing the risk for BPD (33). The shorter duration of non-invasive ventilation observed in the NHFOV group might have contributed to the reduction in BPD. Moreover, NHFOV does not induce glottal constrictor muscle activity, in contrast to NCPAP, thereby obtaining sufficient gas exchange and reducing the risk of apnea (34). Another study found that NHFOV significantly reduced the occurrence of apnea in newborns (35). Our study also showed that NHFOV reduced the incidence of apnea, while no significant differences were found in the subgroup analysis by study type or initial or post-extubation respiratory support. Therefore, the benefits of NHFOV for apnea require further study. No increase in serious adverse outcomes (air leaks, NEC, IVH, nasal injury, ROP, PNX and periventricular leukomalacia) was observed in our study.

This meta-analysis has several limitations: the analyzed trials differed in their study designs and participants' clinical characteristics. The causes of respiratory distress were heterogeneous among the participants; however, we were unable to conduct subgroup analyses of the different causes due to the lack of patient data. Finally, no standardized instruments are available to assess intubation risk and IMV across countries.

Conclusions

Our meta-analysis suggests that during initial respiratory support, NHFOV can reduce the intubation rate and BPD risk unlike NIPPV. As post-extubation respiratory support, the reintubation rates should be viewed with caution; however, NHFOV decreased the duration of non-invasive ventilation and the incidence of abdominal distention. Further studies are needed to explore the potential benefits of NHFOV for respiratory support in extremely preterm or very low-birth weight infants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

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Author Contributions

Protocol development: all authors; literature search and assessing for eligibility: Yong Zhu, Duan Wang; data extraction:Li Ming, Zhifeng Wu; analysis: Li Ming, Zhifeng Wu; critical review and approval of the

manuscript: all authors.

Data Availability Statement

This study is based exclusively on published literature.

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Figure Legends

Fig. 1. PRISMA flow diagram of the identification and selection of trials; CNKI; VIP, Very Important Paper.

Fig. 2. Results of the meta-analysis of intubation rates; NHFOV, noninvasive high-frequency oscillatory ventilation; NIPPV, nasal intermittent positive-pressure ventilation

Fig. 3a. Results of the meta-analysis of reintubation rates; NHFOV, noninvasive high-frequency oscillatory ventilation; NIPPV, nasal intermittent positive-pressure ventilation

Fig. 3b. Results of the meta-analysis of reintubation rates within 72 h; NHFOV, noninvasive high-frequency oscillatory ventilation; NIPPV, nasal intermittent positive-pressure ventilation

eFig.1 (Supplementary Material)Risk of bias summary

eFig.2 (Supplementary Material)Risk of bias graph

eFig.3 (Supplementary Material)Results of the meta-analysis of reintubation rates within 7 days; NHFOV, noninvasive high-frequency oscillatory ventilation; NIPPV, nasal intermittent positive-pressure

eFig. 4 (Supplementary Material)Results of the meta-analysis of duration of non-invasive ventilation

eFig. 5 (Supplementary Material)Results of the meta-analysis of total oxygen therapy time

eFig.6 (Supplementary Material)Results of the meta-analysis of LOS

eFig.7a (Supplementary Material)Funnel plot of abdominal distention

eFig.7b (Supplementary Material)Funnel plot of NEC

eFig.7c (Supplementary Material)Funnel plot of nasal injury

eFig.7d (Supplementary Material)Funnel plot of BPD

eFig.7e (Supplementary Material)Funnel plot of duration of noninvasive ventilation

eFig.7f (Supplementary Material)Funnel plot of total oxygen therapy time

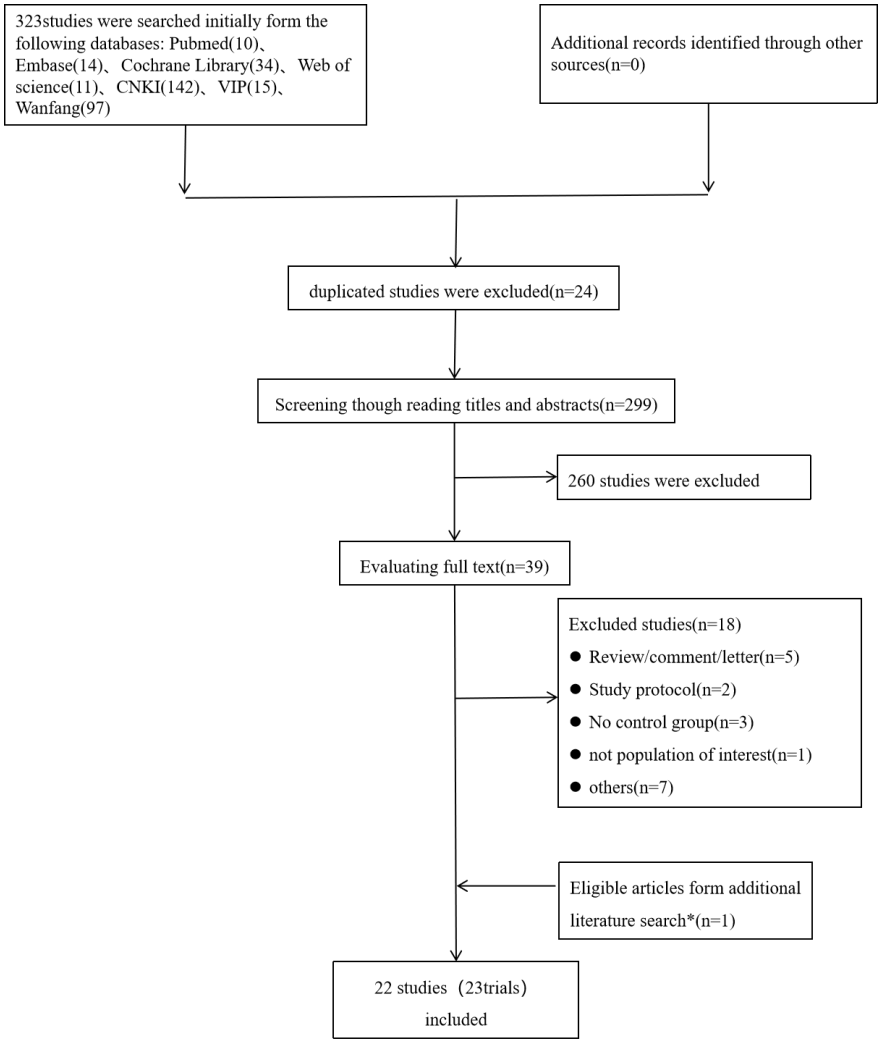
Table

Table 1. Characteristics of the 22 included trials that compared NHFOV with NIPPV

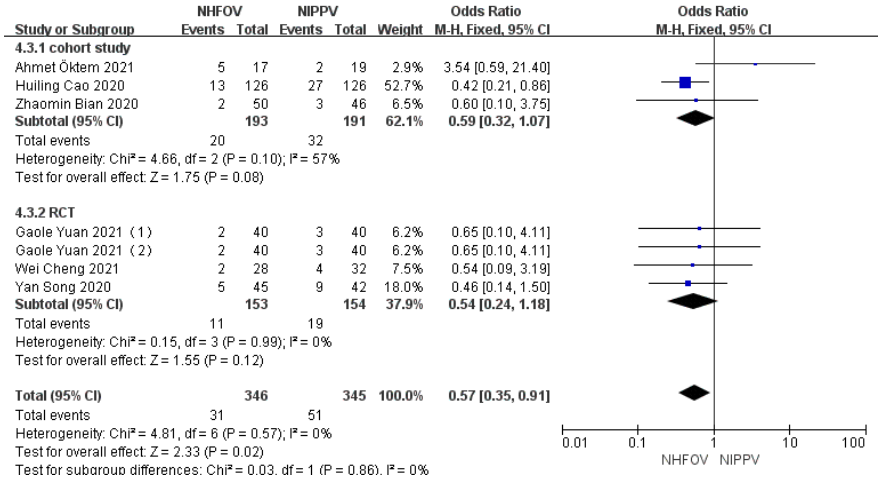
Table 2 Results of the sensitivity analysis

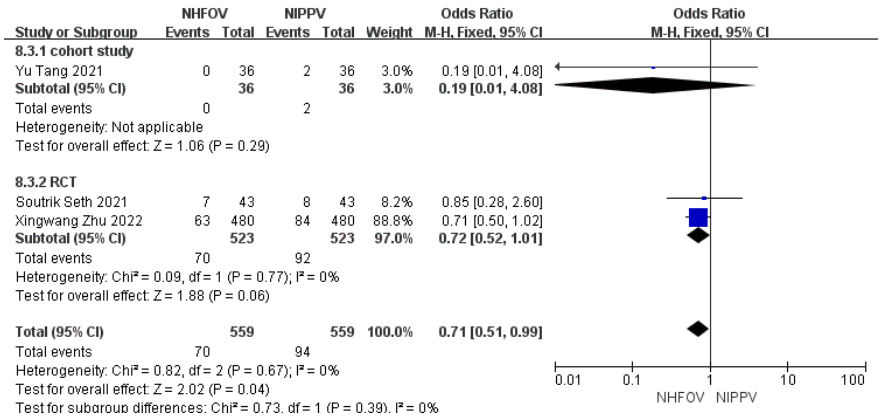
eTable1(Supplementary Material) Results of the meta-analysis of blood gas analysis index(PaO2、PaCO2 and SpO2FiO2 ratio)

eTable2(Supplementary Material) Results of the meta-analysis of adverse outcomes



*The additional literature search was performed on 4/30/2022 to incorporate any newly published title after the initial literature search (performed on 4/1/2022)





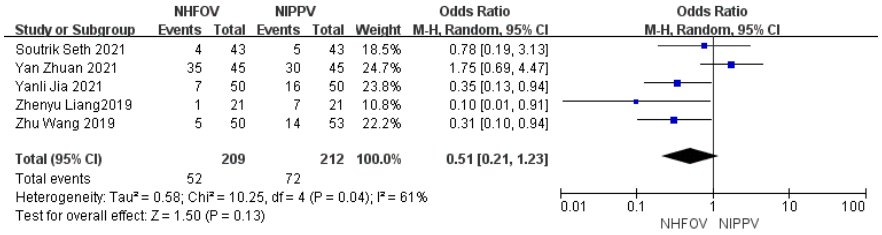


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Table 2 Results of the sensitivity analysis.docx available at https://authorea.com/users/483942/articles/569872-use-of-nhfov-versus-nippv-for-the-respiratory-support-of-preterm-newborns-a-meta-analysis

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