ARTICLE

Elective high frequency oscillatory ventilation versus conventional mechanical ventilation on the chronic lung disease or death in preterm infants administered surfactant: a systematic review and meta-analysis

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BACKGROUND: Use of elective high frequency oscillatory ventilation (HFOV) compared with conventional mechanical ventilation (CMV) results in a small reduction in the risk of chronic lung disease (CLD) or death, but the evidence is weak. Our objective was to explore whether elective HFOV was associated with less CLD or death as compared with CMV in preterm infants administered surfactant.

METHODS: We conducted a systematic review and meta-analysis, including 1835 ventilated participants from 11 randomized controlled trials comparing elective HFOV with CMV between February 1993 and February 2014. The primary outcome was the incidence of CLD or death.

RESULTS: Compared with CMV, elective HFOV was associated with less CLD or death (relative risk (RR) 0.76, 95% confidence interval (CI) 0.61–0.94, $p = 0.01$) ($p = 0.01$, $I^2 = 55\%$), CLD (RR 0.71, 95%CI 0.53–0.93, $p = 0.01$) ($p = 0.03$, $I^2 = 50\%$), and ≥2nd stages of retinopathy of prematurity (RR 0.77, 95%CI 0.62–0.94, $p = 0.01$) ($p = 0.42$, $I^2 = 0\%$). In the subgroup of > 1 dose of surfactant, compared with CMV, elective HFOV was also related to less CLD or death (RR 0.87, 95%CI 0.77–0.98, $p = 0.02$) ($p = 0.10$, $I^2 = 42\%$). No differences were found in the incidences of death, grade 3 or 4 of intraventricular hemorrhage, periventricular leukomalacia, airleak and necrotizing enterocolitis between the two groups.

CONCLUSION: Elective HFOV is superior to CMV in reducing the incidence of CLD or death in ventilated preterm infants administered surfactant, especially in the subgroup of >1 dose of surfactant.

TRIAL REGISTRY: International Prospective Register of Systematic Reviews: No.: CRD42022301033; URL: https://www.crd.york.ac.uk/PROSPERO/.

Journal of Perinatology; https://doi.org/10.1038/s41372-024-02185-x

INTRODUCTION

An animal study has demonstrated that, compared with conventional mechanical ventilation (CMV), high frequency oscillatory ventilation (HFOV) significantly improved lung function in pulmonary mechanics out to 28 days, and resulted in less pulmonary inflammation during the recovery phase of respiratory distress syndrome (RDS) [1]. However, several randomized controlled trials (RCTs) and subsequent meta-analyses have shown inconsistent results [2, 3]. The underlying cause is unclear.

Exogenous surfactant replacement remains a key treatment for preterm infants with RDS [4]. In contrast, no studies have demonstrated benefits of surfactant in adult [5] and pediatric [6] acute respiratory distress syndrome (ARDS), as well as perinatal neonatal ARDS (nARDS) [7, 8]. Importantly, these RCTs were all performed in the pre-nARDS era (before August, 2017), in which the nARDS definition was not available before 2017 [9]. Therefore, it may be a reasonable speculation that perinatal nARDS was considered to be RDS in the pre-nARDS era, and a mixture of different ratios of RDS and nARDS in these studies resulted in the inconsistency. Additionally, comparisons from the pre-surfactant era might also induce heterogeneity when mixed among the studies in the era of surfactant [10, 11].

We have found that surfactant use decreased the incidence of in-hospital mortality, but ≥2 doses of surfactant is related to the increased mortality as compared with ≤1 dose of surfactant in newborn infants with perinatal nARDS [8]. In the present study, we aimed to explore whether elective HFOV was associated with less chronic lung disease (CLD) or death as compared with CMV in preterm infants administered surfactant.

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Received: 25 February 2024 Revised: 13 November 2024 Accepted: 19 November 2024
Published online: 02 December 2024

METHODS

The protocol of the systematic review and meta-analysis was registered in PROSPERO (CRD42022301033) before the search for studies began. Additionally it was performed conforming to the Methodological Expectations of Cochrane Intervention Reviews (MECIR) [12] and was shown in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

Types of studies, eligibility criteria and interventions

The criteria for trials to be included in the meta-analysis were as follows: (1) randomized controlled trials in ventilated preterm infants, (2) trial comparing elective HFOV and CMV, (3) surfactant was used. We did not restrict studies according to language, and searched for studies written in any language from January 1980 to June 2023.

Primary and secondary outcome measures

The primary outcome was to determine whether elective HFOV was associated with less chronic lung disease (CLD, defined as ventilator and/or oxygen dependence at a post-conceptual age of 36-–37 weeks) [14] or death as compared with CMV in preterm infants administered surfactant. The secondary outcomes included death, CLD, airleak, retinopathy of prematurity (ROP) ≥2nd stage [15], necrotizing enterocolitis (NEC) ≥2nd stage [16], intraventricular hemorrhage (IVH) >2nd grade [17], and periventricular leukomalacia (PVL) [18].

Two subgroups were divided and compared: (1) > 1 dose of surfactant; (2) ≤ 1 dose of surfactant.

Literature search, data collection and assessment

A systematic literature search was conducted in June 2023 (Supplementary Table 1), using the methods of the Cochrane Collaboration for Systematic Reviews of Interventions [19]. We searched studies included in PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, Chinese National Knowledge Infrastructure (CNKI), and Wanfang Data Information Site.

Following keywords: "high-frequency oscillatory ventilation" and "preterm" or "infant" and "surfactant" were used. Other neonatal experts were asked to identify any unpublished or ongoing trials, and no studies were identified. Meanwhile, the search was limited to humans. We applied the Cochrane sensitivity-maximizing and Cochrane sensitivity and precision-maximizing strategies as our special search strategies [19].

The obtained studies through the search strategies above were imported to an electronic bibliographic management program using EndNote 21.0 (Endnote, Stanford, CT, USA) and processed them as described in Higgins 2019 [20]. We reviewed the titles and abstracts of the remaining articles and excluded those that were unrelated to our topic or did not meet the eligibility criteria. The full text versions were obtained for the relevant articles that could be included in the review. We tried to contact authors of each included study for further information including surfactant administration and CLD or death, but no response was obtained.

The search strategies, article extraction, and data analysis were performed independently by two reviewers (XY, QT). Data analysis included study design, study interventions, number of subjects in each group, demographic characteristics, inclusion and exclusion criteria, primary and secondary outcomes, and variables used to assess study quality. The two reviewers resolved discrepancies through discussion, with an additional reviewer (LC) involved if needed.

Risk of bias

We used the standard method of conducting a systematic review, as described in the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Risk of Bias tool [21] was used to assess the methodological quality of the included studies. Two independent reviewers evaluated the validity and design characteristics of each study for significant sources of bias, which included allocation concealment (low risk of bias: telephone or central randomization; consecutively numbered sealed opaque envelopes; high risk of bias:open random allocation; unsealed or non-opaque envelopes, alternation; date of birth; unclear risk of bias), sequence generation (low risk of bias: any truly random process, e.g. random number table; computer random-number generator; tossing a coin, minimization; high risk of bias: any non-random process, e.g. odd or even date of birth; hospital or clinic record number; quasi-randomized studies were excluded from the review; unclear risk of bias: unclear description or no description of randomization sequence generation), blinding of participants, researchers and outcomes assessors (low, high or unclear risk of bias for participants; low, high or unclear risk of bias for personnel; low, high or unclear risk of bias for outcome assessors), incomplete data outcomes (low risk of bias: there were no missing data or reasons for missing data were balanced across groups; high risk of bias:missing data were likely to be related to outcomes or were not balanced across groups; unclear risk of bias: there was insufficient reporting of attrition or exclusions to permit a judgment to be made), free of selective reporting (low risk of bias: it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported; high risk of bias: not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported; unclear risk of bias), and free of other bias (low, high and unclear). Each item was assessed as yes (low risk of bias), no (high risk of bias), or unclear (investigators were unable to determine on the basis of available data). It is particularly noted that this study assessed the blinding of participants, researchers, and outcome assessors as low risk, since blinding in neonates is not meaningful, and blinding the personnel is impractical.

Statistical analyses

The Cochrane Risk of Bias tool was applied to assess the methodological quality of the included studies. Discrepancies between the two reviewers were resolved by discussion, with an additional reviewer (Long Chen) involved if needed. Meta-analysis was performed using the Cochrane statistical package RevMan 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). To assess heterogeneity, I^2 distribution and Higgins I^2 statistics were calculated to determine the percentage of total variation across studies resulting from heterogeneity. I^2 statistics was interpreted using the Cochrane Handbook of Systematic Reviews of Interventions: (1) 0–40%: might not be important; (2) 30–60%: may represent moderate heterogeneity; (3) 50–90%: may represent substantial heterogeneity; (4) 75–100%: considerable heterogeneity [20]. Fixed-effects models were employed, and random-effects models were applied based on the assumption that the true effects of the intervention are varying across the included studies. The I^2 statistics was used as an additional measure to describe the extent of heterogeneity, and possible sources of heterogeneity were analyzed [22]. For categorical data, effects were expressed as relative risk (RR), and for continuous data the effect is expressed as the weighted mean difference (WMD). For each measure the 95% confidence interval (CI) was routinely given. Subgroup analyses were interpreted in a similar way.

RESULTS

Description of the included studies

Generally, 19 trials were identified, of which 8 were excluded for the following reasons: the studies by HIFI study groups. 1989 [10] and Clark et al. 1992 [11] were not included because surfactant was not used. the studies by Lista et al. 2008 [23], Van Reepts et al. 2003 [24], Vento et al. 2005 [25], Thome et al. 1998 [26], Johnson et al. 2002 [27] and Craft et al. 2003 [28] were also excluded for the use of high-frequency flow interruption ventilation. Finally, 11 eligible studies and 1835 participants were included in the subsequent analysis [29–39] (Fig. 1).

Figure 2A, B summarized the methodological quality and risk of bias assessments of the included studies. Table 1 summarized clinical characteristics of the included studies and more detailed description were in Supplementary Table 2.

The primary and secondary outcomes

Compared with CMV, elective HFOV was associated with less CLD or death (RR 0.76, 95%CI 0.61–0.94, $p = 0.01$) ($p = 0.01$, $I^2 = 55\%$) (Fig. 3), CLD (RR 0.71, 95%CI 0.53–0.93, $p = 0.01$) ($p = 0.03$, $I^2 = 50\%$), and ≥2nd stages of retinopathy of prematurity (RR 0.77, 95%CI 0.62–0.94, $p = 0.01$) ($p = 0.42$, $I^2 = 0\%$). No differences were found in the incidences of death, 3 or 4 grades of intraventricular hemorrhage, periventricular leukomalacia, airleak and necrotizing enterocolitis between the two groups (Supplementary Figs. 1–9)

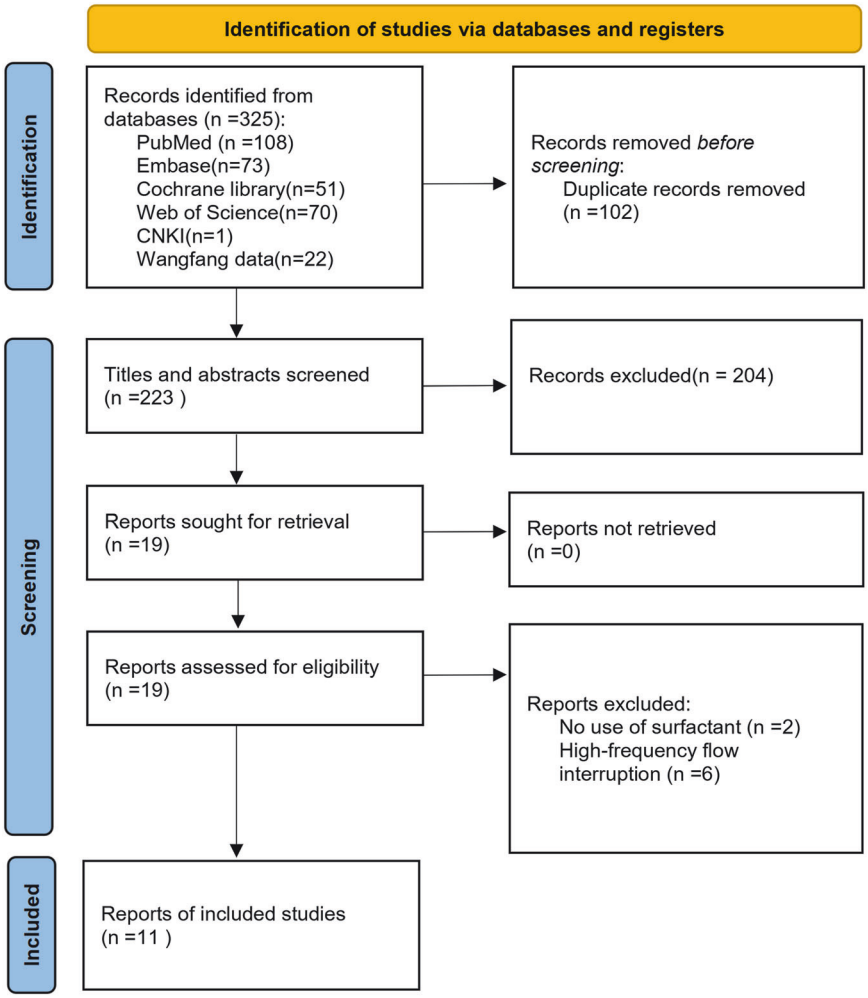

Fig. 1 Study flow diagram. The study selection processes are illustrated, covering the stages of identification, screening and inclusion of studies.

Subgroup analysis

In the subgroup of >1 dose of surfactant, compared with CMV, elective HFOV was associated with less CLD or death (RR 0.87, 95% CI 0.77–0.98, $p = 0.02$) ($p = 0.10$, $I^2 = 42\%$) (Fig. 4).

Publications bias

The funnel plot asymmetry was assessed using Egger's test. As a result, the funnel plot did not demonstrate publication bias in the 11 studies referring to the incidences of CLD or death ($p = 0.221$) (Fig. 2C).

DISCUSSION

In the present systematic review and meta-analysis, we aimed to explore whether elective HFOV was associated with less CLD or death as compared with CMV in preterm infants administered surfactant. As a result, we found that, compared with CMV, elective HFOV was related to less CLD or death (RR 0.76, 95% CI 0.61–0.94, $p = 0.01$). It was consistent with the theoretical advantages of HFOV over CMV and previous animal studies [1].

We also showed that, in the subgroup of >1 dose of surfactant, elective HFOV was associated with less CLD or death as compared with CMV (RR 0.87, 95% CI 0.77–0.98, $p = 0.02$). A retrospective study included neonates of 22–28 weeks' GA in the Canadian Neonatal Network and the results showed that, comparing with 1 dose of surfactant ($n = 3545$), > 1 dose of surfactant ($n = 2018$) were associated with increased incidences of BPD or death (82% vs. 59%, $p < 0.01$), BPD (76% *vs*. 53%, $p < 0.01$), death (26% vs. 13%, $p < 0.01$), stage 3 or higher or treated ROP (27% *vs*. 14%, $p < 0.01$), length of invasive respiratory support (20 vs. 7, $p < 0.01$), severe neurological injury (19% vs. 10%, $p < 0.01$) [40]. Our previous multicenter study has shown that ≥2 doses of surfactant is associated with increased mortality as compared with ≤ 1 dose of surfactant in newborn infants with perinatal nARDS [8]. These preterm infants administered >1 dose of surfactant showed more severe RDS based on FiO_2 level, oxygenation index and radiography than those administered 1 dose of surfactant [41]. It is therefore a possible speculation that these preterm infants administered > 1 dose of surfactant may be perinatal nARDS, less likely RDS. Our result indicates that elective HFOV is the preferred choice when invasive ventilation is needed in the era of surfactant, especially in preterm infants administered >1 dose of surfactant.

Up to now, several studies have compared the beneficial effect of elective HFOV and CMV on CLD or death in ventilated preterm infants, and the results were inconsistent. In 2001, Durand et al. reported that, compared with CMV, early HFOV significantly decreased the incidence of CLD or death in 48 preterm infants with 501–1200 g of birth weight (41.7% vs. 75%, RR 0.56, 95% CI 0.33–0.94) [31]. Gerstmann et al. also showed that, early HFOV reduced the incidence of CLD or death as compared with CMV in 35 weeks' GA or less (26.6% vs 47.5%, RR 0.56, 95%CI 0.34–0.91) [32]. Sun et al. showed that the incidence of CLD or death was significantly higher in the early HFOV group as compared with CMV group (9.6% vs. 22.9%, RR 0.42, 95%CI 0.25–0.71) in the preterm infants with GA less than 32 weeks [39]. In the present study,

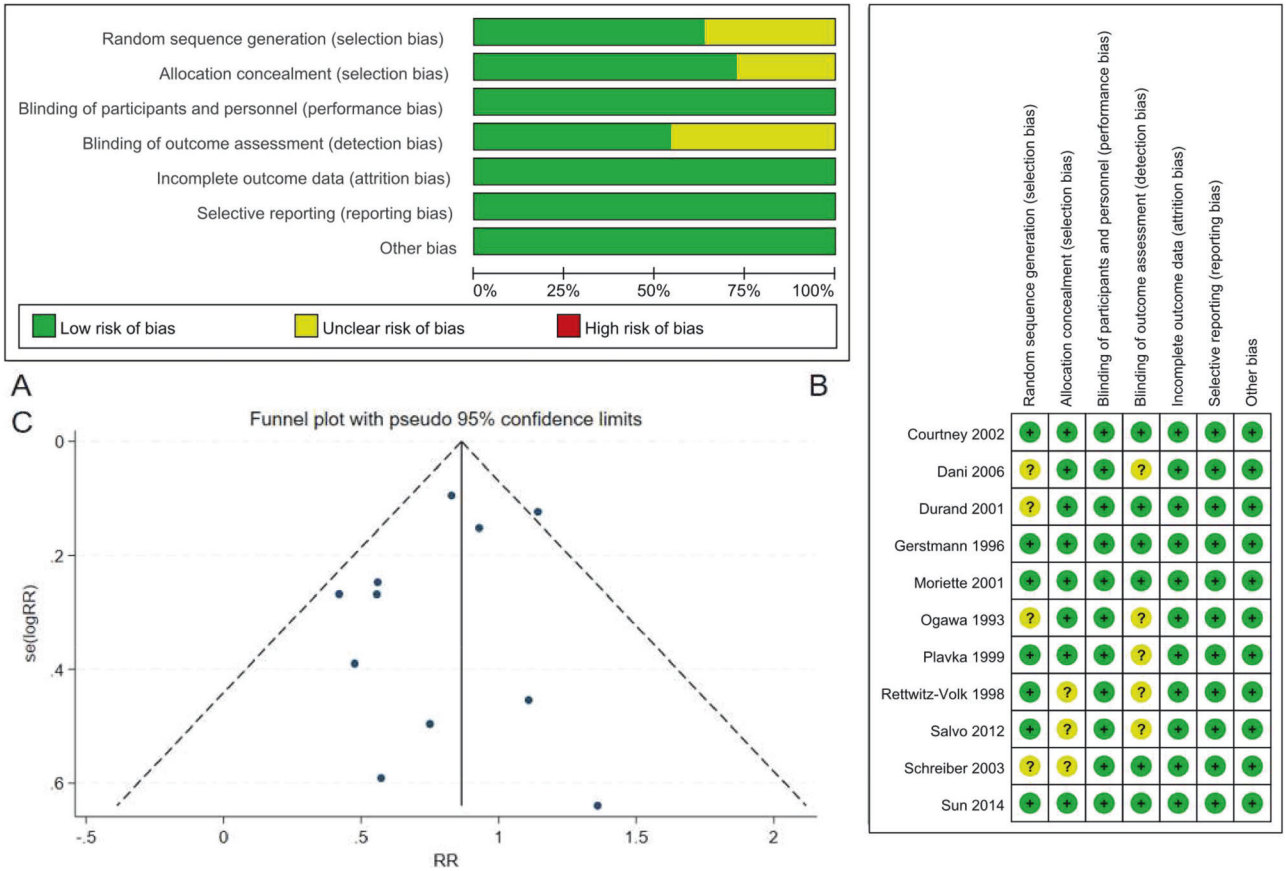

Fig. 2 The risk of bias and funnel plot. A, **B** Review of authors' judgments about each risk of bias item for each included study with low, unclear, and high risk of bias for each feature from the Cochrane Risk of Bias Tool. **C** This figure presents a funnel plot depicting the relationship between the risk ratio and its standard error across multiple studies to access potential publication bias.

elective HFOV was found to reduce the incidence of CLD or death compared with CMV. And these findings are consistent with the meta-analysis by Cool et al.(RR 0.90, 95% CI 0.84-0.97) [3]. and the studies by Courtney et al.(RR 0.83, 95% CI 0.69–1.00) [29]. In contrast, there were no differences found in the study by Dani et al.(RR 1.11, 95% CI 0.45–2.70) [30], Moriette et al.(RR 0.93, 95% CI 0.69–1.25) [33], Plavka et al.(RR 0.48, 95% CI 0.22–1.02) [35], Rettwitz-Volk et al.(RR 1.36, 95% CI 0.39–4.75) [36], Salvo et al.(RR 0.75, 95% CI 0.28–1.98) [37], and Schreiber et al.(RR 1.14, 95% CI 0.90–1.45) [38], which were consistent with another meta-analysis(45% vs. 47%, RR 0.95 95% CI 0.88–1.03) [2]. Nowadays, when ventilated preterm infants with RDS meets the criteria for surfactant therapy, surfactant treatment is administered. Therefore, the study by Clark et al. 1992 [11] was excluded because surfactant was not used, and the meta-analysis did not show difference in the incidence of CLD or death between the two groups (RR 0.86, 95% CI 0.74–1.00) ($p = 0.002$, $I^2 = 56\%$) [3]. (supplementary Fig 10).

The first cause to explain the heterogeneity among different studies may be the diagnosis of respiratory distress and its severity. Studies included in this review were all performed in the pre-nARDS era. A plausible speculation is that several preterm infants with perinatal nARDS might be considered as RDS and different ratios of RDS and perinatal nARDS result in the heterogeneity among these studies. RDS and perinatal ARDS are two different diseases and they should be therefore compared independently, as well as their severities. Among the trials included, the diagnoses of these included preterm infants was different. The diagnosis in the studies by Moriette et al. [33], Dani et al. [30], Salvo et al. [37], Plavka et al. [35], Gerstmann et al. [32]. and Schreiber et al. [38]. were "RDS" while it was "severe RDS" in the study by Sun et al. [15]. But the studies by Durand et al. [31], and Courtney et al. [29], did not present the diagnosis. Furthermore, the key clinical characteristics of RDS and perinatal nARDS often overlap, including the etiology, pathophysiology, diagnosis and treatment [42]. Our previous study in perinatal nARDS demonstrated that perinatal nARDS and RDS were presented together in 30.3% neonates [8].

The second cause to explain the heterogeneity may be the types of HFOV ventilators. Cool et al. [2, 3]. performed two meta-analyses and the conclusions were inconsistent. Further investigation found that the titles of both meta-analyses were "high frequency oscillation ventilation", however, high-frequency flow interruption ventilation (HFFI) was also included. Actually, HFOV and HFFI are two different high frequency respiratory modes and exhibit some important differences in the delivered pressure amplitude and tidal volume [43]. In contrast, HFOV has an active expiratory phase produced by a vibrating piston or membrane over a continuous gas flow or by an electronically controlled cyclic flow reversal. While HFFI does not have an active expiratory phase due to the cyclic opening-closure of one or more pressure valves [44]. After excluding the studies referring to HFFI and surfactant was not administered, HFOV reduced the incidence of CLD or death as compared with CMV in the present study.

The third cause to explain the heterogeneity might be the criteria of using surfactant and redosing, and they were different among these studies. It was "all infants included" in the studies by Courtney et al. [29], Dani et al. [30], Durand et al. [31], Gerstmann et al. [32]. Moriette et al. [33], Salvo et al. [37], and Schreiber et al. [38]. and they were "$PaO_2/FiO_2 < 200$ after 2 h of ventilation" by Sun et al. [15], "clinical diagnosis of RDS" by Ogawa et al. [34],

Table 1. the study characteristics and detail of the included study.

	No. ofcenters	No. of patients		Gestational age (weeks)		Birth weight (kg)		Male (n, %)		prenatal steroids (n,%)		Apgar 5 min		Cesarean section (n,%)		age at randomization		Surfactant use(n,%)		Postnatal steroids		Cross-over	
		HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV	HFOV	CMV
Courtney et al. [29]	26	244	254	26.0 ± 1.6	26.1 ± 1.6	0.86 ± 0. 16	0.85 ± 0. 16	127 (52)	141 (55)	196 (80)	205 (81)	7	7	144 (59)	150 (59)	2.7 h	2.7 h	2.3	2.1	46%	55%	10%	19%
Dani et al. [30]	1	13	12	28.3 ± 1.5	28.0 ± 1.3	1. 13 ± 0. 17	1.08 ± 0.31	6 (46)	7 (58)	11 (85)	9 (75)	7.4(6, 9)	7.5 (6, 9)	8 (62)	9 (85)	0.75 ± 0.15 h	0.78 ± 0. 13 h	1.9	2	—	—	—	—
Durand et al. [31]	7	26	24	25. 9 ± 2. 1	26.1 ± 1.7	0.82 ± 0.22	0.86 ± 0.21	—	—	11 (42)	12 (50)	—	—	—	—	2.8 ± 1.2 h	2.4 ± 1.0 h	2	2.3	42%	62%	8%	29%
Gerstmann et al. [32]	3	64	61	30.8 ± 2.2	30.1 ± 2.7	1.56 ± 0.46	1.46 ± 0.47	44 (68.8)	33 (54. 1)	19 (30)	11 (18)	8 (8, 9)	8.5 (8, 9)	40 (62.5)	40 (65.5)	Mean 2.9 h	Mean 2.0 h	1.2	1.8	—	—	2%	15%
Moriette et al. [33]	10	139	134	27.5 ± 1.4	27.6 ± 1.5	0.98 ± 0.22	1.00 ± 0.25	82 (59)	77 (57)	72 (52)	74 (55)	—	—	71 (51)	76 (57)	2.42 ± 1.58 h	2.37 ± 1.97 h	1.3	1.6	54%	52%	15%	29%
Ogawa et al. [34]	9	46	46	29.0 ± 2.3	29.0 ± 2. 1	1.24 ± 0.32	1.26 ± 0.32	28 (61)	27 (59)	—	—	6.9 ± 2.1	7.5 ± 1.8	—	—	2.0 ± 1.6 h	1.7 ± 1.5 h	—	—	—	—	9%	2%
Plavka et al. [35]	1	22	21	26 ± 1.8	26 ± 1.6	0.82 ± 0. 18	0.85 ± 0. 19	15(79)	8 (44)	10(53)	9 (50)	7 (5, 9)	7 (6, 9)	—	—	< 20 min	< 20 min	0.6	1.9	1.6 mg/kg (0 to 11.3)	2.75 mg/kg (0 to 17.5)	0%	10%
Rettwitz-Volk et al. [36]	3	46	50	28.5 ± 0.9	28.4 ± 0.95	1. 11 ± 0. 11	1. 11 ± 0. 12	22 (48)	31 (62)	36 (78)	32 (64)	—	—	46 (100)	47 (94)	1. 16 ± 0.50 h	0.66 ± 0.33 h	>1	>1	43%	60%	17%	18%
Salvo et al. [37]	3	44	44	26.4 ± 2.2	26.5 ± 3.2	0.87 ± 0.27	0.91 ± 0.22	13 (30)	12 (27)	—	—	—	—	28 (64)	28 (64)	within 2 h	within 2 h	1.1	2	2.5%	10.2%	2.3%	2.3%
Schreiber et al. [38]	1	102	105	—	—	—	—	—	—	—	—	—	—	—	—	—	—	> 2.0	> 2.0	—	—	—	—
Sun et al. [39]	2	177	179	29.3 ± 2.5	29.5 ± 2.3	1. 13 ± 0.20	1. 12 ± 0.24	112 (65)	116 (63)	136 (77)	131 (73)	7.7 ± 1.1	7.5 ± 1.2	—	—	5.8 ± 5.0 h	5.9 ± 5. 1 h	≥0.5	≥0.8	—	—	0%	0%

HFOV high frequency oscillation ventilation, *CMV* conventional mechanical ventilation, △*P* pressure amplitude, "-" no data available.

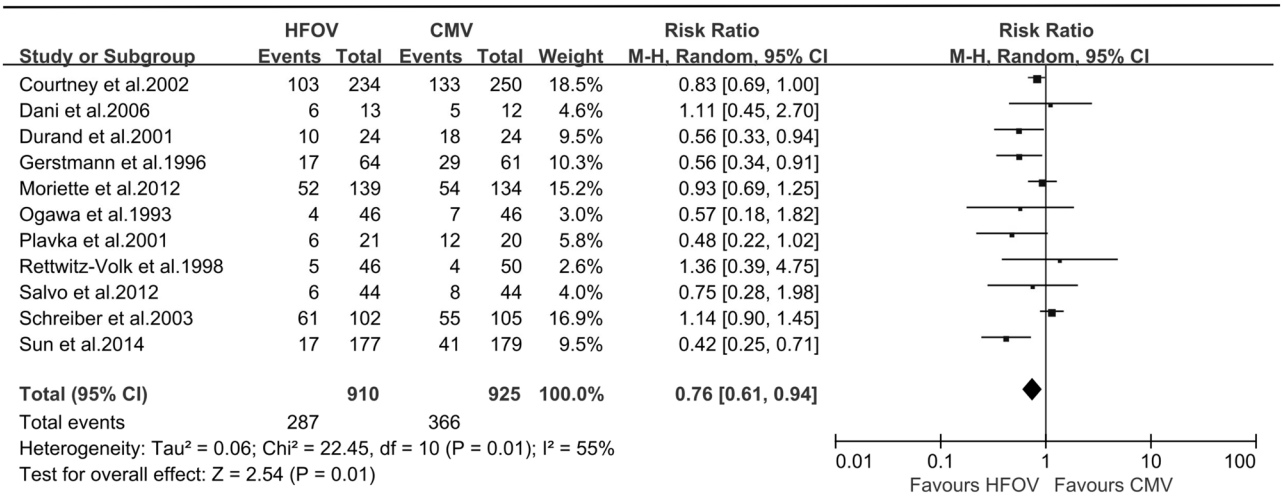

Fig. 3 Forest plot of pooled Risk Ratio (RR) and 95% CIs for all studies. Comparison of chronic lung disease or death in preterm infants with pulmonary surfactant between high frequency oscillatory ventilation and conventional mechanical ventilation.

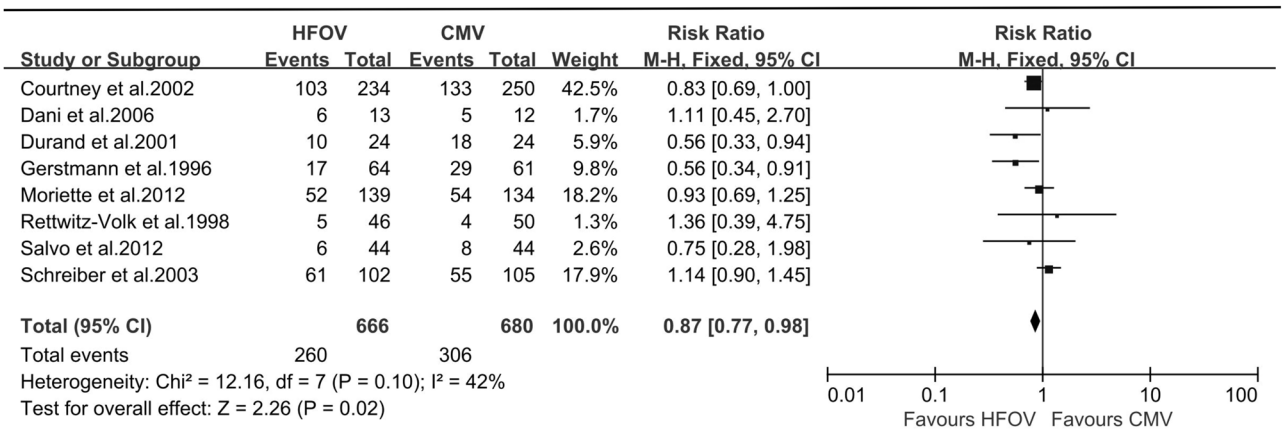

Fig. 4 Forest plot of pooled Risk Ratio (RR) and 95% CIs for studies administered more than 1 dose of surfactant. Comparison of chronic lung disease or death in preterm infants with more than 1 dose of pulmonary surfactant between high frequency oscillatory ventilation and conventional mechanical ventilation.

"chest x-ray showed RDS grade II and $FiO_2 > 0.60$" by Rettwitz-Volk et al. [36], and "HFOV:$FiO_2 > 0.35$ or PAwDP ≥ 12 in infant weigh ≥ 1 kg; PAwDP > 10 in infant weigh < 1 kg CMV: $FiO_2 \geq 0.35$" by Plavka et al. [35], otherwise, the criteria for administration of the second surfactant was also different and the details were described in Table 1. At last, the optimal dose for perinatal nARDS also remains unknown and needs further study.

Furthermore, our study also showed that, compared with CMV, elective HFOV was also associated with less CLD (RR 0.71, 95%CI 0.53–0.93, $p = 0.01$). It was consistent with the meta-analysis (RR 0.86, 95%CI 0.78–0.9) [3]. However, when the study by Clark et al. 1992 [11] was excluded for no use of surfactant, the meta-analysis also showed difference in the incidence of CLD between the two groups (RR 0.88, 95%CI 0.79–0.98) ($p = 0.01$, $I^2 = 49\%$) (Supplementary Fig 11).

The major limitations of the present study: (1) The included studies were performed in the pre-nARDS era with a long study period, and advances in obstetric and neonatal medicine may result in inconsistencies of baseline characteristics. Therefore, the results need to be further verified in the nARDS era. (2) The long span of gestational age from 24 to 34 weeks. Smaller gestational age is more easily influenced by several comorbidities and their interaction. (3) The mean/medium value of surfactant did not reflect the actual need of individual infant. Individual patients' data could not be obtained and compared between the two groups. (4) The most recent publication included in the meta-analysis was from 2014. Since then, invasive ventilation has been changed, including HFOV plus volume guarantee and CMV plus volume guarantee. They might induce potential bias, including restricted application scope. These problems could be overcome in additional studies. Recently, we organized a multicenters, randomized controlled trials regarding comparing elective HFOV and CMV as primary respiratory support modes in preterm infants with perinatal nARDS (NCT03591796) (registration time: July 10, 2018), and the results could give us more reasonable explanations.

In summary, compared with CMV, elective HFOV was associated with less CLD or death.Further studies in the nARDS era were needed to verify the results.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ACKNOWLEDGEMENTS

We thank The First Research foundation of Young Neonatologist of China International Medical Foundation-New Seeding Initial (Z-2019-41-2101-04). The Combined Study Program of Health Committee and Bureau of Science and Technology of Chongqing (2022MSXM001). Long Chen have no financial disclosure, and the other authors also have indicated they have no financial relationships relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

XY and QT accomplished the article-extracting and data analysis, drafted the initial manuscript and reviewed the manuscript. JL and YS reviewed the manuscript. LC conceptualized and designed the study, funding acquisition, project administration and supervision, critically reviewed the manuscript for important intellectual content.

All authors revised the manuscript and approved the final manuscript as submitted. LC verified the underlying study data. All authors have full access to the data in the present study and accept responsibility for submitting it for publication.

FUNDING

The First Research foundation of Young Neonatologist of China International Medical Foundation-New Seeding Initial (Z-2019-41-2101-04). The Combined Study Program of Health Committee and Bureau of Science and Technology of Chongqing (2022MSXM001).

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was not requested because this study retrieved and synthesised data from already published studies.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41372-024-02185-x.

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