



# HFOV vs CMV for neonates with moderate-to-severe perinatal onset acute respiratory distress syndrome (NARDS): a propensity score analysis

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## Abstract

This study aimed to evaluate whether high-frequency oscillatory ventilation (HFOV) could reduce mortality and the incidence of bronchopulmonary dysplasia (BPD) of perinatal-onset neonatal acute respiratory distress syndrome (NARDS) compared with conventional mechanical ventilation (CMV). Medical records were collected and retrospectively analyzed. Among the 700 neonates with NARDS who needed invasive ventilation, 501 (71.6%) received CMV, while 199 (28.4%) received HFOV. One-to-one propensity score matching (127:127) was used to match the baseline characteristics of patients who received CMV and HFOV. The results showed that birth weight and oxygenation index (OI) were independently associated with mortality in the multivariate logistic regression. No significant differences were observed in mortality or the incidence of BPD between the two groups. The incidence of intraventricular hemorrhage (IVH) and ventilation-free days were significantly lower in the HFOV group than in the CMV group (3.9 vs 11.80%,  $p=0.02$ ; 15.226 vs 20.967 days,  $p=0.01$ ). There were no significant differences between the two groups regarding other secondary outcomes.

**Conclusion:** HFOV was associated with a decreased incidence of IVH in infants with NARDS compared with CMV. However, there were significantly more VFDs in the CMV group than in the HFOV group, and HFOV did not appear to be superior to CMV in decreasing the mortality and incidence of BPD in infants with NARDS.

## What is Known:

- The diagnostic criteria of neonatal acute respiratory distress syndrome (Montreux criteria) were established in 2017.
- To date, studies comparing high-frequency oscillatory ventilation and conventional mechanical ventilation in the treatment of neonatal acute respiratory distress syndrome are insufficient.

## What is New:

- High-frequency oscillatory ventilation did not appear to be superior to conventional mechanical ventilation in decreasing the mortality and incidence of bronchopulmonary dysplasia in infants with moderate-to-severe perinatal-onset neonatal acute respiratory distress syndrome.
- High-frequency oscillatory ventilation was associated with a decreased incidence of intraventricular hemorrhage in infants with moderate-to-severe perinatal-onset acute respiratory distress syndrome compared with conventional mechanical ventilation.

**Keywords** NARDS · HFOV · CMV · Neonates

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## Abbreviations

ARDS	Acute respiratory distress syndrome
BPD	Bronchopulmonary dysplasia
CMV	Conventional mechanical ventilation
FiO <sub>2</sub>	Fraction of inspired oxygen
HFOV	High-frequency oscillatory ventilation
IVH	Intraventricular hemorrhage
IQR	Interquartile range
MAS	Meconium aspiration syndrome
NARDS	Neonatal acute respiratory distress syndrome
NICU	Neonatal intensive care unit
NEC	Necrotizing enterocolitis
OI	Oxygenation index
PPHN	Persistent pulmonary hypertension of the newborn
PEEP	Positive end-expiratory pressure
PSM	Propensity score matching
PDA	Persistent ductus arteriosus
PROM	Premature rupture of membranes
PARDS	Pediatric acute respiratory distress syndrome
PICUs	Pediatric intensive care units
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
RCTs	Randomized controlled trials
RDS	Respiratory distress syndrome
VLBW	Very low birth weight
VG	Volume-guarantee
VFDs	Ventilation-free days

## Introduction

The diagnostic criteria of acute respiratory distress syndrome (ARDS) in children and adults have been widely recognized, while the diagnostic criteria of neonatal acute respiratory distress syndrome (NARDS) were not developed until 2017 (Montreux criteria) [1]. NARDS is associated with meconium aspiration, sepsis and infectious pneumonia, pulmonary hemorrhage, perinatal asphyxia complicated by severe respiratory failure, and biliary pneumonia according to the Montreux criteria [1]. A study in late preterm and term infants showed that the incidence of ARDS is approximately 28.8% [2].

Invasive mechanical ventilation, including conventional mechanical ventilation (CMV) and high-frequency oscillatory ventilation (HFOV), is an effective method for the treatment of ARDS in critically ill neonates. With its combined advantages of delivering small tidal volumes with low phasic pressure changes at supraphysiologic frequencies [3], stable/higher mean airway pressure, and avoiding gas trapping, HFOV may be associated with improved lung protection. In addition, studies of HFOV in children also showed benefits in short-term oxygenation, although no improvement in clinical outcomes was observed [4]. However, the results of some

previous human trials comparing the two modes of ventilation remain inconclusive [5].

To date, there are insufficient studies comparing HFOV and CMV in the treatment of NARDS, and the clinical outcomes of CMV and HFOV in the treatment of neonates with respiratory failure are inconsistent; therefore, we conducted this retrospective study to compare the mortality and incidence of bronchopulmonary dysplasia (BPD) between neonates with moderate-to-severe perinatal-onset NARDS who received HFOV and CMV.

## Materials and methods

### Patient selection

This retrospective study was conducted in the Department of Neonatology, Children's Hospital of Chongqing Medical University, China. The data were collected from the medical records of the Department of Neonatology from 1 January 2014 to 31 October 2018. Ultimately, 700 neonates (gestational age of 24 weeks 0 day to 42 weeks 0 days) with perinatal-onset moderate-to-severe NARDS who received HFOV or CMV within 24 h after birth were enrolled.

### Inclusion criteria

For a neonate to be included, the following four criteria had to be fulfilled: (1) gestational age between 24 + 0 and 42 + 0 weeks; (2) diagnosis of NARDS; and (3) moderate-to-severe NARDS and invasive ventilation within 24 h after birth.

### Exclusion criteria

Neonates meeting at least one of the following criteria were not eligible for the study: (1) neonates who only needed non-invasive ventilation; (2) neonates with major congenital anomalies or chromosomal abnormalities; (3) neonates with upper respiratory tract abnormalities; (4) neonates with pulmonary adenomatous malformations, sequestration, congenital diaphragmatic hernia, or pulmonary hypoplasia; or (5) neonates with crossover between CMV and HFOV.

### Intervention

Indications of invasive ventilation include respiratory failure (including respiratory acidosis, arterial blood gas pH <7.2 and PaCO<sub>2</sub> >60 mmHg; hypoxemia, PaO<sub>2</sub> <50 mmHg under auxiliary oxygen supply or under noninvasive ventilation; fraction of inspired oxygen (FiO<sub>2</sub>) >40%; severe apnea) [6].

The indications for CMV mechanical ventilation in this study were as follows [7]: (1) PaO<sub>2</sub> <50 mmHg, (2) PaCO<sub>2</sub> >60 mmHg, (3) intractable or recurrent apnea, (4) gasping or

poor respiration, (5)  $O_2$  saturation <85% on supplemental oxygen.

The indications for HFOV mechanical ventilation in this study were as follows [8]: insufficient carbon dioxide elimination, respiratory acidosis (i.e., pH <7.20–7.25); and/or hypoxemia ( $PaO_2$  <50 mmHg)/hypercarbia ( $PaCO_2$  >60 mmHg); apnea/bradycardia; increasing respiratory distress; high fractional oxygen requirement. HFOV was for primary use not rescue in this study.

### Ventilation strategies

Infants assigned to CMV received ventilation with Servo-i and SLE 5000 ventilators. Conventional ventilation was delivered by time-cycled, pressure-limited ventilators starting with a rate of 30–40 breaths per minute and an inspiratory time of 0.4 s. The aimed tidal volumes were 4–6 ml/kg, and positive end-expiratory pressure (PEEP) was 5–8 mmHg.

Infants assigned to HFOV received ventilation with the SensorMedics 3100A and SLE 5000 ventilators. The open lung strategy was used in this study. There was no crossover to HFOV or CMV in this study. Patients were ventilated with the selected ventilation modes (HFOV or CMV) through the treatment period.

Tube diameters were chosen according to the patient's weight. Ventilator settings were adjusted at the discretion of the attending clinician to maintain arterial oxygen saturation, as measured by pulse oximetry, between 88 and 96%, a  $PaO_2$  between 50 and 80 mm Hg, a  $PaCO_2$  between 35 and 55 mm Hg, and a pH between 7.20 and 7.45. Analysis of the first blood gas was performed at admission, monitored every 6–18 h for 24 h, and then monitored daily until the infant was extubated. Chest radiography was performed immediately at admission and was reviewed daily for 2 to 3 days and then once every 5 to 7 days until extubation. Chest ultrasound was performed after admission and was reviewed daily for 2 to 3 days and then once every 5 to 7 days until extubation. Echocardiography was performed within 24 h after admission. If required, echocardiography was performed again at any time.

Extubation criteria are as follows: pH >7.20,  $PaCO_2$  <55 mmHg,  $Paw$  6  $cmH_2O$ ;  $FiO_2$  0.30; sufficient spontaneous breathing effort without any clinical and radiologic sign of respiratory distress, per clinical evaluation [9].

### Definition of the important diagnoses and concepts

The diagnosis of NARDS was made according to the criteria established by the Montreux conference in 2017 [1]: acute onset; oxygenation impairment with reduced end expiratory lung volume requiring positive pressure to recruit the alveoli; respiratory failure not fully explained by lung edema due to heart failure; and diffuse bilateral opacities with loss of

aeration on chest radiographs. The following neonatal respiratory disorders qualify for a diagnosis of ARDS: meconium, milk, bile, blood, or water aspiration; lung hemorrhage; and infectious or biliary pneumonia. Acute processes occurring in extrapulmonary organ systems that might trigger acute respiratory failure via systemic inflammatory responses and thus meet ARDS criteria, such as early- or late-onset sepsis, fetal inflammation, perinatal asphyxia, and necrotizing enterocolitis.

Moderate-to-severe perinatal-onset NARDS was determined by the use of the oxygenation index (OI) and triggers, including perinatal asphyxia, early-onset sepsis, and other perinatal factors that occurred in the first 24h of life. Severe NARDS was determined by an OI of  $\geq 16$ , and moderate NARDS was determined by an OI between 8 and 16 [1].

Diagnostic criteria for pneumonia, MAS, and aspiration were according to the references [[1, 10]].

Diagnostic criteria for the following outcomes were according to the literature: bronchopulmonary dysplasia (BPD) [11], retinopathy of prematurity (ROP) [12], NEC [13], intraventricular hemorrhage (IVH) [14], and ventilation-free days (VFDs) [15].

### Data collection

Data collected included demographics (i.e., gestational age, sex, birth weight, age at admission, and age at NARDS diagnosis), perinatal factors (premature rupture of membranes [PROM] and triggers sepsis, pulmonary hemorrhage, MAS, pneumonia, aspiration of blood, and perinatal asphyxia), elements of NARDS (i.e., disease severity and type of ventilation), 5-min Apgar score, lactate at admission, strategies during hospitalization (i.e., surfactant use), primary outcomes (i.e., death rate and BPD), and secondary outcomes (i.e., IVH  $\geq$  3rd stage, ROP  $\geq$  2nd, NEC  $\geq$  2nd stage, air leak, duration of invasive ventilation, ventilation-free days, and duration of hospitalization).

Data were obtained from the clinical records and were collected daily on web-based case report systems provided by Open CDMS. All data were collected from the electronic medical record.

Primary outcomes were neonatal intensive care unit (NICU) mortality and the incidence of BPD. Secondary outcomes included complications during hospitalization, such as IVH  $\geq$  3rd stage, ROP  $\geq$  2nd stage, NEC  $\geq$  2nd stage, air leakage, duration of invasive ventilation, ventilation-free days, and duration of hospitalization.

### Statistical analysis

All data were analyzed using SPSS 23.0 software (Chicago, IL, USA). The results are presented as the median (interquartile range [IQR]) for continuous variables and the number (%)

for categorical variables. The normality of the data distribution was tested with the Kolmogorov-Smirnov test. Independent continuous variables were analyzed using *T* tests, and categorical variables were analyzed using chi-square or Fisher's exact tests. A *p* value <0.05 was considered statistically significant.

Propensity score matching (PSM) was estimated using a logistic regression model in which the following covariates were included: gestational age, sex, birth weight, age at admission, age at NARDS diagnosis, perinatal factors (PROM and triggers sepsis, pulmonary hemorrhage, MAS, pneumonia, aspiration of blood, and perinatal asphyxia), OI, surfactant use, prenatal glucocorticoid, postnatal glucocorticoid, 5-min Apgar score, and lactate at admission. Those covariates were selected based on the previous literature in which an association between those indicators and mortality and the incidence of BPD in adults and PARDS was reported [16–18]. A 1:1 “nearest neighbor” case-control match without replacement was used [19]. Each neonate who received CMV was matched with the neonate who received HFOV and who had the closest estimated propensity scores. Post-match variables were compared between the groups using univariate and multivariate analysis. The variables that were considered to have a univariable association ( $p < 0.2$ ) with mortality were included in multivariate logistic regression analysis to determine the independent factors of mortality ( $p < 0.05$ ). After each step of the multivariate analysis, we evaluated the collinearity by starting with a correlation matrix if the addition of the new variable had a large effect on the point estimate for another parameter in the model. When variables were highly correlated, the variable with the highest univariable association with the outcome in the multivariate analysis was retained. All analyses were verified by three statisticians (LC, JX, and SQX).

## Results

### Clinical characteristics of neonates with NARDS

Between 1 Jan 2014 and 31 Oct 2018, 40,176 infants were admitted to the Department of Neonatology, Children's Hospital of Chongqing Medical University. Among them, 3302 infants suffered from respiratory failure and needed invasive mechanical ventilation, and the total number of infants who needed assisted ventilation, including noninvasive and invasive mechanical ventilation, was 5691. Ultimately, 700 infants met the criteria for entry (199 cases were assigned to HFOV and 501 cases to CMV) (Fig. 1).

The characteristics of the two groups before and after matching are shown in Tables 1 and 2. Before matching, 8 out of the 17 covariates, including sex, age at admission, prenatal glucocorticoid use, postnatal glucocorticoid use, 5-min

Apgar score, OI, pulmonary hemorrhage, and pneumonia, were significantly different between the two groups. After matching, 254 cases were included in the PSM model. All 17 covariates were well balanced, and no significant differences were observed (Tables 1 and 2).

### Mortality and BPD

Before matching, the overall mortality of neonates with NARDS was 18.5% (130 of 700), and the incidence of BPD was 19% (133 of 700). After matching, the mortality of neonates with NARDS was 25.2% (64 of 254), and the incidence of BPD was 19.2% (49 of 254). There were no significant differences in mortality or the incidence of BPD between the two groups (25.2 [32 of 127] vs 25.2% [32 of 127];  $p = 1.000$  and 16.5 [21 of 127] vs 22.0% [28 of 127];  $p = 0.266$ ) (Table 3). In particular, the death rate of neonates with severe NARDS was 40.47% (51/126), while that of neonates with moderate NARDS was 10.23% (13/127) after matching.

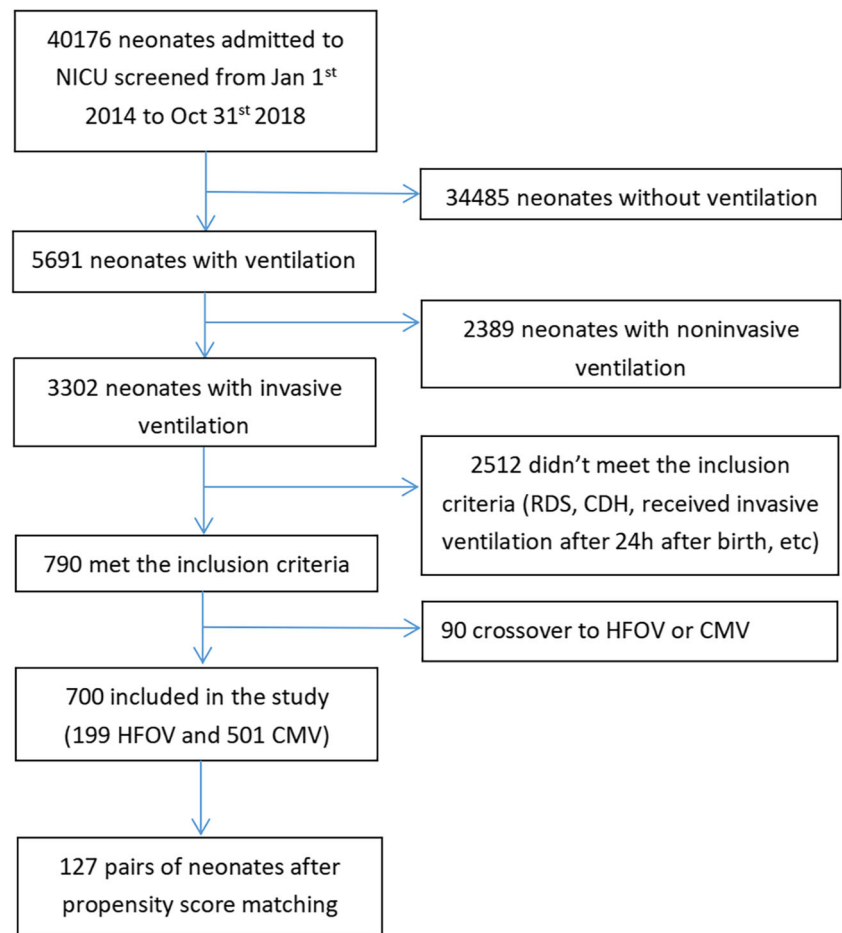
### Secondary outcomes

There were no significant differences between the two groups regarding the other secondary outcomes, including air leakage, ROP, NEC, surfactant treatment, PDA treatment, duration of invasive ventilation, and duration of hospitalization (Table 3). The incidence of IVH ( $\geq 3$ rd stage) was significantly lower in the HFOV group than in the CMV group (3.9 vs 11.8%,  $p = 0.020$ ). The VFDs in the CMV group was significantly higher than that in the HFOV group (20.96 vs 15.22 days,  $p = 0.01$ ).

### Univariate and multivariate analyses of neonate mortality at NARDS diagnosis

Univariate and multivariate analyses were performed to identify the risk factors that were associated with neonate mortality at NARDS diagnosis, and the results are shown in Tables 4 and 5.

In univariate analysis, variables at the diagnosis of NARDS that were considered to have a univariable association with mortality included gestational age, birth weight, age at admission, 5-min Apgar score, OI, lactate at admission, PROM, pneumonia, aspiration of blood, and perinatal asphyxia, with a *p* value of less than 0.2 (Table 4). Furthermore, in multivariate analysis, variables at diagnosis of NARDS that retained an independent association with mortality included birth weight and OI. The factors associated with higher mortality were lower birth weight and higher OI (Table 5).

**Fig. 1** Flowchart of study enrollment

## Discussion

Our study is the first to compare the mortality, incidence of BPD, and other complications between neonates with NARDS who received either CMV or HFOV. Our data suggest that there were no significant differences in mortality or the incidence of BPD between the CMV and HFOV groups.

PARDS occurred in approximately 6% of all mechanically ventilated children in pediatric intensive care units (PICUs) internationally [20], while in our study, NARDS occurred in approximately 12% (700/5691) of all mechanically ventilated infants in the NICU. The relatively higher incidence may be associated with unique triggers for respiratory failure (e.g., MAS, perinatal asphyxia) during the neonatal period that might differ from pediatric ARDS and variations in specific aspects of developmental lung biology and maturation and neonatal immune status [1]. In our study, the mortality of neonates with NARDS before matching was 18.5%, and the mortality of neonates with NARDS was 25.2% after matching. However, data on the mortality of neonates with NARDS are lacking, and more studies reporting on the mortality of neonates with NARDS are needed. In this study, severe NARDS ( $OI \geq 16$ ) was associated with higher mortality

than moderate NARDS ( $8 \leq OI < 16$ ). In the Montreux definition,  $OI$  is recommended to determine hypoxemia severity [1], and hypoxemia severity is closely associated with mortality. A meta-analysis comparing HFOV and CMV revealed that there is no difference in mortality for acute pulmonary dysfunction in preterm infants. Likewise, in our study, no significant difference was observed in mortality between the CMV and HFOV groups after matching.

In our study, after matching, the incidence of BPD was 16.5% and 22.0% in the CMV and HFOV groups, respectively. Although BPD is mostly associated with premature birth, it can also occur in infants born at late preterm or term infants who need aggressive ventilator therapy for severe acute lung disease and in infants with risk factors for BPD, including infection, maternal hypertension or preeclampsia, patent ductus arteriosus (PDA) [21], and antenatal corticosteroid rate. In our study, the median gestational ages of neonates after matching were 34.86 weeks in the CMV group and 34.86 weeks in the HFOV group. The reasons for the relatively high rate of BPD might be that all the neonates enrolled in our study received invasive ventilation; among them, the incidence of early-onset sepsis was high, with rates of 34.6% in the CMV group and 33.1% in the HFOV group. However, the



**Table 1** Baseline characteristics of neonates in CMV and HFOV groups

	Before matching			After matching		
	CMV (n=501)	HFOV (n=199)	p value	CMV (n=127)	HFOV (n=127)	p value
Gestational age, weeks	34.0 (31.3, 37.8)	35.4 (31.1, 38.7)	0.157	34.86 (31.71, 38.71)	34.86 (31.00, 38.71)	0.615
Gender (male), no. (%)	294 (58.7)	133 (66.8)	0.046	41 (43.2)	86 (54.1)	0.092
Birth weight, g	2130 (1505, 2960)	2300 (1550, 3100)	0.071	2200 (1520, 3000)	2310 (1380, 3050)	0.888
Age at admission, h	2.4 (1.67, 5.54)	3.25 (1.7, 7.7)	0.024	2.78 (1.67, 8.00)	3 (1.71, 7.35)	0.954
Age at NARDS diagnosis, h	34.49 (27.77, 40.94)	34.10 (28.83, 42.61)	0.708	34.56 (27.15, 42.40)	33.71 (28.19, 41.20)	0.891
PROM (yes), no. (%)	147 (29.3)	60 (30.2)	0.832	36 (28.3)	36 (28.3)	1.000
Prenatal glucocorticoid (yes), no. (%)	136 (27.1)	38 (19.1)	0.026	22 (17.3)	23 (18.1)	0.869
Postnatal glucocorticoid (yes), no. (%)	6 (1.19)	10 (5.02)	0.002	2 (1.57)	6 (4.72)	0.281
5' Apgar score	8.43 (7.17, 9.45)	8.67 (7.58, 9.62)	0.026	8.56 (7.38, 9.53)	8.73 (7.55, 9.67)	0.347
OI	10.4 (8.3, 15.1)	16.9 (12.5, 24)	0.000	15.60 (10.40, 20.00)	16.00 (11.10, 20.00)	0.773
Lactate at admission, mmol/L	3.6 (2.4, 5.4)	3.7 (2.5, 5.6)	0.630	3.933 (2.57, 5.6)	3.963 (2.493, 5.483)	0.985

Data are presented as median (IQR), or number (%)

CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; IQR, interquartile range; MAS, meconium aspiration syndrome; NARDS, neonatal acute respiratory distress syndrome; OI, oxygenation index; PROM, premature rupture of membranes

administration rate of prenatal glucocorticoids was low, with rates of 17.3% in the CMV group and 18.1% in the HFOV group.

The effects of HFOV or CMV on neurological outcomes are controversial. Some RCTs reported similar brain injury in neonates who received HFOV or CMV [22]. Cools et al. [5] reported that although increased risks of severe grade IVH and periventricular leukomalacia (PVL) were found in some studies, the overall meta-analysis revealed no significant differences in those effects between the HFOV and CMV groups. In our study, the incidence of IVH was higher in the CMV group than in the HFOV group. However, we did not show a long-term

neurodevelopmental outcome in our study, and a long-term follow-up of neurodevelopmental outcomes is necessary. In our study, there were no significant differences in the incidence of air leakage, ROP, NEC, duration of invasive ventilation, or duration of hospitalization between the two groups, which was in agreement with the findings of previous studies reporting acute pulmonary dysfunction or respiratory distress syndrome (RDS) in preterm infants [5]. Our results also showed that there were significantly more VFDs in the CMV group than in the HFOV group. However, comprehensively considering the ability to reduce ventilator-dependent time and mortality, this result failed to show a benefit of HFOV in this respect.

**Table 2** Triggers of NARDS in CMV and HFOV groups

	Before matching			After matching		
	CMV (n=501)	HFOV (n=199)	p value	CMV (n=127)	HFOV (n=127)	p value
Triggers (yes), no. (%)						
Sepsis	163 (32.5)	70 (35.2)	0.504	44 (34.6)	42 (33.1)	0.791
Pulmonary hemorrhage	139 (27.7)	77 (38.6)	0.005	46 (36.2)	44 (34.6)	0.793
MAS	15 (2.9)	11 (5.5)	0.110	8 (6.3)	7 (5.5)	0.790
Pneumonia	115 (22.9)	26 (13.0)	0.003	22 (17.3)	23 (18.1)	0.869
Aspiration of blood	37 (7.4)	9 (4.5)	0.168	5 (3.9)	6 (4.7)	0.758
Perinatal asphyxia	32 (6.4)	6 (3.0)	0.076	4 (3.1)	6 (4.7)	0.519

Data are presented as number (%)

CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; MAS, meconium aspiration syndrome; NARDS, neonatal acute respiratory distress syndrome

**Table 3** Primary and secondary outcomes of neonates in CMV and HFOV groups after propensity score matching

	CMV (n=127)	HFOV (n=127)	p value
Primary outcomes			
Death (yes), no. (%)	32 (25.2)	32 (25.2)	1.000
BPD (yes), no. (%)	21 (16.5)	28 (22.0)	0.266
Secondary outcomes			
IVH ≥ 3rd (yes), no. (%)	15 (11.8)	5 (3.9)	0.020
ROP ≥ 2nd (yes), no. (%)	1 (0.8)	2 (1.6)	1.000
NEC ≥ 2nd (yes), no. (%)	2 (1.6)	0 (0.0)	0.498
Air leak (yes), no. (%)	3 (2.4)	7 (5.5)	0.334
Surfactant treatment (yes), no. (%)	81 (63.8)	79 (62.2)	0.795
PDA treatment (yes), no. (%)	6 (4.72)	5(3.93)	0.758
Duration of invasive ventilation, h	114.54 (62.05, 182.85)	149.47 (63.69, 325.03)	0.060
Ventilation free days, days	20.967 (0.000, 24.354)	15.226 (0.000, 22.291)	0.010
Duration of hospitalization, days	17.91 (9.13, 29.63)	17.83 (5.50, 33.50)	0.813

Data are presented as median (IQR), or number (%)

BPD, bronchopulmonary dysplasia; CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; IVH, intraventricular hemorrhage; IQR, interquartile range; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity

There were no differences in the triggers of NARDS between the two groups after matching. In this study, the main triggers were sepsis and pulmonary hemorrhage. The rates of sepsis were 34.6% in the CMV group and 33.1% in the HFOV

group after matching. Randolph et al. [23] reported that the most common trigger was infection in children with ARDS. Goh et al. [24] reported that the rate of sepsis in children’s ARDS triggers was 43%, while Dahlem et al. [25] reported a rate of 34%. The reported incidence of neonatal sepsis varies from 7.1 to 38 per 1000 live births in Asia [26, 27]. By comparison, rates reported in the USA and Australasia range from 1.5 to 3.5 per 1000 for early-onset sepsis [28]. This reminds us that although neonatal perinatal ARDS has its own unique trigger factors, such as MAS and asphyxia, similar to pediatric ARDS, sepsis is still an important trigger factor, especially in Asia. More attention should be paid to sepsis by clinical neonatal physicians. In addition, the rates of pulmonary hemorrhage were 36.2% in the CMV group and 34.6% in the HFOV group after matching. The exact pathogenesis of pulmonary

**Table 4** Univariate logistic regression analysis for mortality of neonates at NARDS diagnosis

	OR	95% CI	p value
Gestational age, weeks	0.865	0.822–0.910	<0.001
Gender (male)	0.913	0.619–1.347	0.647
Birth weight, g	0.999	0.999–1.000	<0.001
Age at admission, hours	0.959	0.914–1.005	0.081
Age at NARDS diagnosis, hours	1.007	0.987–1.027	0.478
PROM	1.644	1.104–2.448	0.014
Prenatal glucocorticoid	0.967	0.616–1.518	0.883
Postnatal glucocorticoid	0.000	0.000	0.998
5’ Apgar score	0.775	0.706–0.850	<0.001
OI	1.106	1.708–1.134	<0.001
Lactate at admission	1.9.03	1.037–1.153	<0.001
Sepsis	0.831	0.549–1.256	0.379
Pulmonary hemorrhage	1.235	0.825–1.849	0.304
MAS	0.791	0.265–2.335	0.671
Pneumonia	0.541	0.313–0.935	0.028
Aspiration of blood	0.399	0.141–1.133	0.085
Perinatal asphyxia	6.267	3.202–12.267	<0.001

CI, confidential interval; MAS, meconium aspiration syndrome; NARDS, neonatal acute respiratory distress syndrome; OR, odds ratio; OI, oxygenation index; PROM, premature rupture of membranes; PDA, patent ductus arteriosus

**Table 5** Multivariate logistic regression analysis for mortality of neonates at NARDS diagnosis

	OR	95% CI	p value
Gestational age, weeks	0.865	0.822–0.910	<0.001
Birth weight, g	0.999	0.999–1.000	0.038
PROM	1.374	0.857–2.205	0.187
5’ Apgar score	0.889	0.761–1.039	0.138
OI	1.119	1.087–1.151	<0.001
Lactate at admission	1.069	0.997–1.145	0.059
Pneumonia	0.839	0.450–1.564	0.580
Perinatal asphyxia	2.705	0.902–8.105	0.076

CI, confidential interval; NARDS, neonatal acute respiratory distress syndrome; OR, odds ratio; OI, oxygenation index

hemorrhage remains unknown; some studies have described that it is associated with hypoxemia, sepsis, and PDA [29]. Further exploration is still needed to define the triggers of NARDS.

Multivariate analysis found that birth weight and OI trend were the most significant factors associated with mortality. An RCT on ARDS in adults conducted by Derdark et al. [30] also reported that the OI trend was the most significant post-treatment predictor of survival irrespective of the assigned ventilator. In a recent randomized trial for pediatric ARDS, the severity of hypoxia was measured by the OI, and the average mortality in children with an OI  $\geq 13$  at study entry was 36 vs 20% in those with an OI  $\leq 12$  [23]. In this study, the mortality of patients with severe NARDS (OI  $\geq 16$ ) was 40.47%, which was higher than that of patients with moderate NARDS ( $8 \leq \text{OI} < 16$ ), which was 10.23% after matching.

Many factors, related to both the intervention itself and the individuals, could interact in complex ways. The disease severity, clinical management, ventilator properties, and clinical interventions warrant further exploration of outcomes with a multivariate modeling approach. Considering the patient's clinical features, physiological status, and response to ventilatory support to determine how to optimally ventilate the patient is of great importance [31]. A study showed that the use of a reduced tidal volume and avoidance of high airway pressures were associated with improved mortality when compared with a conventional ventilatory approach [32]. Adequate use of either mode of ventilation is crucial for neonatologists, and the importance of applying an optimal lung recruitment strategy during HFOV and monitoring and controlling tidal volume with the VG during conventional ventilation should be considered [32, 33]. A new ventilator strategy, HFOV combined with VG, has also been demonstrated to be a potential strategy to prevent lung injury [34].

There are several limitations in this study, including the following: (1) the relatively small number of patients; (2) this was a single-center study in Chinese newborns; (3) it was a retrospective paper, and Chan et al. [35] concluded that many questions remained unanswered, and HFOV should be compared to CMV in a large randomized, controlled trial; (4) propensity score matching (PSM) can balance more variables at the same time, which can only be limited to the known confounding variables, and some unknown confounding variables may still have an impact on the final result; (5) there was a lack of assessment of long-term neurodevelopmental outcomes; and (6) patients enrolled in our study who received invasive ventilation and patients with NARDS who were undergoing noninvasive ventilation were excluded.

According to the Montreux criteria, early-onset sepsis and NARDS perinatal triggers are defined by those occurring in the first 72h of life. In this study, we aimed to explore whether HFOV was superior to CMV in decreasing mortality and the incidence of BPD in infants with NARDS. To reduce various

types of heterogeneity and confounding factors, we targeted neonates with moderate-to-severe NARDS that occurred in the first 24h of life. Late-onset sepsis was defined as a positive result on one or more blood cultures obtained after 72h [36]. The onset time of NEC usually occurs on the 3rd or 4th day of life in term neonates, and the onset time may be delayed for up to three or 4 weeks in preterm neonates [37]. NARDS triggered by late-onset sepsis or NEC may be ventilated after 24h. Therefore, those with NARDS triggered by late-onset sepsis or NEC were excluded. Thus, our study results could not apply to NARDS triggered by late-onset sepsis or NEC and other types of NARDS. Taken these limitations into account, this retrospective study may have some implications for clinical practice and future research on HFOV vs CMV in infants with perinatal-onset NARDS.

In summary, in this retrospective study, our results showed that HFOV was associated with reduced IVH in neonates with moderate-to-severe perinatal-onset NARDS compared with CMV. However, VFDs in the CMV group were significantly higher than those in the HFOV group and did not appear to be superior to CMV for decreasing mortality and the incidence of BPD in neonates with moderate-to-severe perinatal-onset NARDS.

**Authors' contributions** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Long Chen, Jing Xiong, and Shuqin Xie. The first draft of the manuscript was written by Kaizhen Liu. The manuscript was revised by Yuan Shi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Data availability** Yuan Shi is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data will be made available upon request.

## Declarations

**Ethics approval and consent to participate** This study was approved by the Institutional Review Board, Children's hospital of Chongqing Medical University of China. Not applicable

**Consent for publication** Not applicable

**Conflict of interest** The authors declare no competing interest.

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