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# Scoping review of initiation criteria for inhaled nitric oxide in preterm infants after 7 days of age

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# Scoping review of initiation criteria for inhaled nitric oxide in preterm infants after 7 days

## of age

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## ABSTRACT

<b>Objectives</b> : Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH)
associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-
acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy
in this population in the post-acute phase is currently lacking. This study therefore aimed to
identify the criteria for initiating iNO therapy, alongside the associated clinical and
echocardiographic findings, in this population.
<b>Design</b> : We performed a scoping review using the population–concept–context framework
following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
extension for Scoping Reviews.
Data sources: The PubMed, Embase, and the Japanese database "Ichushi" were
systematically searched for relevant articles published between January 2003 and August
2023.
Eligibility criteria: This study included randomized controlled trials, prospective and
retrospective cohort studies, case-control studies, and case series on iNO therapy in the
post-acute phase for preterm infants born before 34 gestational weeks, written in English or
Japanese.

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**Data extraction and synthesis**: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

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Results: We included 14 reports that analyzed the data of 12 separate studies. The utilization of iNO therapy was categorized as prophylactic, rescue, or other modalities. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare. **Conclusion**: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the postacute phase appeared to be safe and devoid of complications. **Trial registration number**: UMIN000051498.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

This scoping review is the first to provide a comprehensive overview of the use of inhaled nitric oxide therapy in preterm infants during the post-acute phase.

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To ensure transparency, this review followed the guidelines of the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

> We conducted a thorough search across three databases, including the Japanese

database "Ichushi," where the most vulnerable preterm newborns with a history of

active resuscitation for years, have been documented.

A quality assessment of the included studies was not performed in this review, as it was beyond the scope of this study's objectives.

# INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.<sup>1, 2</sup> In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.<sup>3, 4, 5</sup> Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns, with studies indicating that newborns with moderate-to-severe BPD may develop hypoxic respiratory failure (HRF) or PH in the post-acute phase, which can be potentially fatal.<sup>6, 7</sup>

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Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.<sup>8, 9, 10</sup> However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase. Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.<sup>11, 12, 13</sup> Similarly, various echocardiographic findings are used to diagnose PH.<sup>7, 14</sup> Echocardiography is

considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.<sup>15</sup> In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

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Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence concerning the initiation criteria for iNO administration after 7 days of life, along with any pertinent associated information.

## METHODS AND ANALYSIS

## **Protocol and registration**

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.<sup>16</sup> This review was conducted in compliance with the published protocol.

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## **Eligibility criteria**

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, https://doi.org/10.46658/JBIMES-20-12). Articles meeting the following eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as

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> randomized controlled trials (RCTs), prospective and retrospective cohort studies, casecontrol studies, and case series. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO
ropulation	after 7 days of age
	Aim to identify the initiation criteria of iNO, postnatal day of the iNO
	initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation
Concept	criteria of iNO therapy, concomitant use of other drugs, and adverse
	effects
	Published between January 2003 and August 2023
	Conducted in developed countries
Context	Published in English or Japanese
	Randomized controlled trial, cohort study, case-control study, and case
	series

 Excluding congenital malformation syndrome and a chromosomal

abnormality

PCC, Population-Concept-Context; iNO, inhaled nitric oxide

## Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,<sup>17</sup> alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix.

## Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.<sup>18</sup> The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,<sup>19</sup> to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough full-

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> text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

## Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form

(Tables 3 and 4).

## Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an

assessment of the risk of bias within the included studies was not undertaken.

## Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were

analyzed. However, neonatologists participated in the review process and discussed the

results.

RESULTS

## Selection of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially eligible studies was subsequently performed, leading to the exclusion of an additional 107 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 18 original records were included in this study.

## Characteristics and results of sources of evidence

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.<sup>8,</sup>

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<sup>9, 11</sup> All of these studies were multicenter and involved a relatively large number of patients,

ranging from 451 to 582. The findings of these included studies are summarized in Table 2.

Гаbl	le 2. Summary	of the findin	gs of the inc	luded studies			U ding f
	Author Year	Study design	Countr y	Setting	Population	Intervention or Concept	9 D Study findings server reig
Stu	idies investiga	ting prophyl	actic iNO us	e for BPD			12024
1	Ballard et al. 2006 <sup>8</sup>	RCT	USA	Multicente r (21 centers)	GA; ≤32 weeks BW; 500– 1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N <sub>2</sub> : n=288	Survo in NO and 36.8 in placebo (RB: 1.23, 95% Cl: 1.01– 1.51 in of the discharged sooner (P=0.04), shore in the source of the s
2	Ballard et al. 2016 <sup>11</sup>	RCT	USA	Multicente r (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	complications of prematurity. Survival without BPD; 36 weeks, 31.3% vs. 347%, RB: 0.98, (95% CI: 0.75–1.28 P=0.69); 40 weeks, 58.7% vs. 54.1%, RB: 1.085(95% CI: 0.92–1.27 P=0.33). There was no difference in serious adverse events, comorbidities of prematurity, and the severity of lung disease a 36 weeks.
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4 5 6 7 8 9 10 11 12 13 14	3	Hasan et al. 2017 <sup>9</sup>	RCT	Canada	Multicente r (33 centers)	GA; <30 weeks Treatment; 5– 14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N <sub>2</sub> : n=175	Survie al without BPD was not improved at 36 weeks. Respective and neurodevelopmental outcome were not different at 18–24 mone of postmenstrual age. There was no difference in the common commentations of prematurity.
15 16 17	Stu	dies investig	sating rescue iN	O use for F	Ъ <sub>р</sub>			iNO ឆ្លាំទីគ្គី a ចាំអាistration between days 7 and
18 19 20 21 22 23 24 25 26	4	Truog et al. 2014 <sup>10</sup>	Retrospectiv e cohort	USA	Multicente r (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at ≥7 days of age	14 way between the second seco
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	5	Hsiao et al. 2019 <sup>20</sup>	Retrospectiv e cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5–2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	Compared BPD (19/27, 70.4%) and second by PH (14/27, 51.9%) The off-bybel iNO use group demonstrated the poorest response and the highest in-hospital mortality (P <0.001).
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6	Nakanishi et al. 2023 <sup>4</sup>	Retrospectiv e cohort	Japan	Multicente r (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Postation in the preterm infants with more severation in the preterm infants with more severation in the preterm infants with more severation in the preterm infants with more severations. Postation is a severation in the preterm infants with more severation in the preterm infants with more severation in the preterm infants with more severations. Postation is a severation in the preterm infants with more severation in the preterm infants with more severations. Postation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation in the preterm infants with more severations. Postation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation is a severation in the preterm infants with more severation
7	Oka et al. 2023 <sup>13</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482– 814) g, (n=30)	iNO after 96 h of age (not for PPHN)	to integraphic reported. Therefore in in-hospital outcome between responders and no responders. Methemoglobinemia (MetHb >5%) did not dictor in any participant. Early in was associated with treatme response (OR: 0.89, 95% CI: 0.7970–
8	Fraga et al. 2023 <sup>14</sup>	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37– 43) at study entry (n=37)	0.995 P=0.04) Thirty (82%) patients had echogar of ographic evidence of PAH befoge in 0, and 19 (56%) after 48 h of iNO (P=0.04). FiO <sub>2</sub> requirements were significantly difference between time points, before E
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3 4 5 6 7 8 9 10 11 12 13 14 15	9	Nakao et al. 2012 <sup>21</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	initiation of iNO and after 48–168 h (P=00)5) Indice to find HRF a to find Out compared Deather was been No compared Backer and
16 17 18 19 20 21 22 23 24 25 26	10	lwatani et al. 2022 <sup>22</sup>	Retrospectiv e cohort	Japan	Multicente r (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Historio Eal CAM (n=9), SGA (<-3 SD) (n=25,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
27 28 29 30 31 32 33 34 35 36 37 38 39	Oth 11	er studies Athvale et al. 2004 <sup>23</sup>	Prospective cohort	USA	Single center	A total of 13 ventilated preterm infants with BW of 500– 1500 g (n=13)	To evaluate the acute effects of low-dose iNO in preterm infants with evolving BPD	iNO gid a ot affect lung compliance, pulmenary resistance, or N <sub>2</sub> clearance. There was a small increase in LVEF (P<0:05) Mean Sp2 remained unchanged, but the duration of spontaneous hypoxemic episode ncreased during iNO (P<0.05).
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12	Di Fiore et al. 2007 <sup>24</sup>	RCT	USA	Multicente r (21 centers)	Ventilated preterm infants with GA of 24. 9 (24–27) weeks and BW of 500–1250 g (n=71)	iNO; n=34 placebo; n=37 for ≥ 24 days at 7–21 days of life	There is a point of the second
13	Hibbs et al. 2008 <sup>25</sup>	RCT	USA	Multicente r (21 centers)	GA; ≤32 weeks BW; 500– 1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=230 N <sub>2</sub> : n=225	Infarit erandomized to INO had less pulmon and provide to INO had less pulmon and provide to INO had less (brom and the provide to INO had less pulmon and the provide to INO had
14	Hussain et al. 2022 <sup>12</sup>	Before–after study	USA	Single center	Before; 32.2±6.5 After; 33.8 ±6.6 (n=67)	Comparing a retrospective control group to a prospective cohort after implementatio n of an iNO weaning protocol	The implementation of an iNO weaning protocols ignificantly decreased iNO usage by approximately 60% (149 h [IQR, 63–23] vs. 59 h [37–122]) (P=0.008)
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6	iNO, inhaled nitric oxide; GA, gestational age; BW, birth weight; RB, relative benefit; Cl, confidenc@int@rval; OR, odds ratio; BPD,
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8 9	bronchopulmonary dysplasia; RCT, randomized controlled trial; PH, pulmonary hypertension; HRF, 🕷 absorb to respiratory failure; LVEF,
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11 12	left ventricular ejection fraction; NRNJ, Neonatal Research Network of Japan; IQR, interquartile rage: AH; pulmonary artery
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All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),<sup>8</sup> while the remaining studies did not demonstrate improvement.<sup>9, 11</sup> None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.<sup>20</sup>

Studies investigating rescue iNO use for HRF and PH Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,<sup>4, 10</sup> four retrospective cohort studies conducted in single tertiary centers,<sup>13, 14, 20, 21</sup> and one multicenter retrospective cohort study.<sup>22</sup> Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.<sup>21, 22</sup> The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.<sup>13</sup> noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also found no difference in the

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incidence of in-hospital outcomes between responders and non-responders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.<sup>4</sup> reported in their retrospective cohort study using the Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.<sup>14</sup> emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

## Other studies

Four studies were included in the analysis, despite not completely aligning with our research concept, as they still provided valuable information. These included two multicenter RCTs,<sup>24, 25</sup> one prospective cohort study conducted in a tertiary center,<sup>23</sup> and a before-and-after comparison study.<sup>12</sup> Additionally, two secondary follow-up analyses of a previous RCT were incorporated. The participant numbers ranged from 13 to 582.

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Among these studies, three included very-low-birth-weight infants as an inclusion criterion,<sup>23, 24, 25</sup> while one included preterm infants.<sup>12</sup> Table 2 provides a summary of the included studies. This subgroup comprised two reports on respiratory function,<sup>23, 24</sup> one on respiratory prognosis at 1 year of age,<sup>25</sup> and one on a quality improvement (QI) project aimed at reducing inappropriate iNO use.<sup>12</sup>

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## 

## Synthesis of results

## Initiation criteria for post-acute iNO

The diagnostic criteria for PH are poorly described, and may not be crucial for postacute iNO use. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.<sup>8, 9, 11</sup> However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.<sup>12, 13, 14, 20, 22</sup> Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.<sup>12, 13, 14, 22</sup> Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.<sup>14</sup> To measure the severity of respiratory compromise, various measures have been utilized. Four studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO<sub>2</sub>]),<sup>8, 11, 12, 25</sup> one utilized the OSI,<sup>13</sup> and two employed the oxygenation index.<sup>12, 21</sup> In out-of-concept studies, Hussein et al. reported the use of echocardiography for PH diagnosis and noted echocardiographic findings, including flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the PFO/PDA level.<sup>12</sup> They also reported a 60% reduction in iNO use following the implementation of a weaning protocol. A summary of these findings is presented in Table 3.

	Author		Initiation criteria	for iNO	
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Other
1	Ballard et al. 2006	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO <sub>2</sub> ×100 /SpO <sub>2</sub>	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting through a PDA. Septal flattening or bowing at end- systole. TPV:RVET ratio, 0.2– 0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.	N/A	N/A

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9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	lwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A
11	Athavale et al. 2004	N/A	N/A	N/A	N/A
12	Fiore et al. 2007	N/A	N/A	N/A	N/A
13	Hibbs et al. 2008	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
14	Hussain et al. 2022	Defined as HRF with signs of pulmonary hypertension on an echocardiogram dictated by a pediatric cardiologist.	<ul> <li>Leftward bowing of the interventricular septum</li> <li>Tricuspid regurgitation</li> <li>Right-to-left or bidirectional shunting at the levels of the patent foramen ovale and patent ductus arteriosus</li> </ul>	Oxygenation index, respiratory severity score (FiO <sub>2</sub> ×MAP)	Eligibility for weaning iNO: iNO $\leq$ 20 ppm, FiO <sub>2</sub> $\leq$ 60%, PaO <sub>2</sub> $\geq$ 60 mmHg, SpO <sub>2</sub> $\geq$ 90%

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO<sub>2</sub>, partial pressure of oxygen; SpO<sub>2</sub>, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

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Details of post-acute iNO administration The starting dose of iNO ranged from 3–20 ppm, with six studies starting at 20 ppm<sup>8, 9,</sup> <sup>11, 20, 24, 25</sup>, and one study reporting a maximum dose of 80 ppm.<sup>20</sup> The duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, five RCTs included a 24-day pre-protocol dosing period.<sup>8, 9, 11, 24, 25</sup> Regarding adjunctive medications, reports involving the use of surfactants,<sup>11, 13, 20</sup> inotropes,<sup>12, 20</sup> corticosteroids<sup>13</sup>, bronchodilators<sup>14</sup>, and diuretics<sup>14</sup> were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm birth,<sup>8, 9, 11, 24, 25</sup> which aligns with the findings of retrospective studies.<sup>4, 12, 13, 21, 22, 23</sup> However, one case of pulmonary edema was reported after 48– 168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.<sup>14</sup> A summary of these data is presented in Table 4.

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Table 4. Summary of the details of post-acute iNO admin	istration in preterm infants in the	BICI	≢ded studies
		<u> </u>	80

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	for uses relation of the second secon	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	2024. Downloade nement Superieu ated to text and c A N	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	ad from http://om ata minage. Surfactag, Al tra	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	jopen.bmj.com/ on June 9, aining, and similar technolc N/	No differences in common complications of prematurity No elevation in NO <sub>2</sub> or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days:	N/A	N/A	2025 at Agence ogies. N/A	N/A
		F	25 For peer review only - http://bmjopen.br	5 nj.com/site/about/	guidelines.xhtml	

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	5	Hsiao et al. 2019	(n=47 or 0.96%) > 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactants (3.7% Beign 227 (3.7% Beign 227 Dopamine to 227 (37.0%) to 22.2% Portage 7 (22.2%) of the second formation of the	N/A	
	6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administration in the late phase of hospitalization)	N/A	26 days [14–70 days]	2.//bmjopen.bmj.com/ on June 9 Al training, and similar technol	N/A	
	7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8– 32.5) days	Surfactant 25 corticosteroia	No complications No methemoglobinemia	
	8	Fraga et al. 2023	40 weeks (37– 43)	20 ppm	N/A	Bronchodilators; n=16 (43%)	Pulmonary edema; n=1	
				26	6	bgraphique o		
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9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	(43%ated to text and N/A and N/A and	No complications	
10	lwatani et al. 2022	39 (12–142) day	N/A	2–36 days	ded from http .ur (ABES) . data mining N/A N/	No methemoglobinemia No jaundice	
11	Athvale et al. 2004	32.1 (16–55) days	10 ppm	2 h	p://bmjopen.b , Al training, a N/A	No changes in head ultrasonography after the study	
12	Fiore et al. 2007	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	mj.com/ on June and similar techn N/A	N/A	
13	Hibbs et al. 2008	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	9, 2025 at Agen lologies. N/A	N/A	
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2 3 4 5 6 7 8 9 10 11 12 13	Before; Hussain et 36.4±8.4 14 al. weeks 2022 After; 35.2 ±6.3 weeks	Before: Starting dose: 10 ppm (63–24 Highest dose: 20 ppm After: (37–12)	Sildenafil, n (26) 8 (22) 149 vs. 2 (6) P 20.08 3) h Milrinone, n 26 20 59 (43) vs. 15 (50 20 20 20 58 2) h Epoprosteno 6 20 20 58 (16) vs. 3 (10 20 20 20 20 20 20 20 20 20 20 20 20 20	No notable negative effects			
14 15 16 17 18	iNO, inhaled nitric oxide		nloaded from perieur (ABES t and data min				
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#### DISCUSSION

#### Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of post-acute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH. Additionally, miscellaneous reports that did not completely fit within the PCC framework, but still provided valuable insights into post-acute iNO use were also categorized.

#### Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006<sup>8</sup> demonstrated the effectiveness of post-acute iNO in promoting survival without BPD, while two other studies did not show significant efficacy.<sup>9, 11</sup> Importantly, large prospective studies reported no adverse events with consistent iNO use.

#### Studies investigating rescue iNO use for PH

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The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,<sup>12, 14</sup> with only four reports utilizing echocardiography as a criterion for diagnosis of PH.<sup>12, 13, 14, 22</sup> However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.<sup>7, 26</sup> Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,<sup>4</sup> may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

## Other studies

In addition to studies focusing on rescue iNO use for PH, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea.

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Considering the rare reporting of complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

Gaps

This scoping review underscores that the utilization of iNO to treat PH in the postacute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. Thus, to promote the use of echocardiographic evaluation for PH before iNO administration, a simple and robust parameter must be identified.

## Strengths and limitations

To our knowledge, this is the first scoping review to explore the use of iNOs in postacute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD

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alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the post-acute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

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## CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of postacute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed

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retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of post-acute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

## **ACKNOWLEDGMENTS**

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## **CONFLICT OF INTEREST**

None declared.

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#### **AUTHOR CONTRIBUTIONS**
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SK and HN conceptualized this study. All authors contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial input for the development of the final version. DS and HN provided feedback on the methodology. All authors have read and revised the draft, and have approved the final version of the manuscript.

# **DATA SHARING STATEMENT**

All data relevant to the study are included in the article or uploaded as supplementary information. elie

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18	Figure 1: Flow diagram showing the study selection process.
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# Supplementary Figure. Search strategy of the scoping review in Pubmed.

Search number	Querv	Sort Bv	Filters	Search Details	Results
				("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm *"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "atomizer *"[Title/Abstract] OR "inhala *"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "inhala *"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "No"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer *"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer *"[Title/Abstract] OR "Notrico Oxide"[MeSH Terms] OR "Nitrico Monoxide"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract:] OR "no-inhalation"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract:] OR "no-inhalation"[Title/Abstract:] AND ("inNO"[Title/Abstract:] OR "no-inhalation"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract:~2] OR "Nitric Oxide"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract:~2] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "Nitric Oxide"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract:~2] OR "Nitric Oxide"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract:~2] OR "Nitric Oxide"[Title/Abstract]] AND ("english"[Language] OR "japanese"[Language]) AND	
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# **BMJ Open**

# Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34

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# ABSTRACT

**Objectives**: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

**Design**: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

**Data sources**: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

**Eligibility criteria**: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

**Data extraction and synthesis**: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

**Results**: We included 10 reports that analyzed the data from 10 separate studies. The use of iNO therapy was categorized as prophylactic and rescue purpose. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute

phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare. **Conclusion**: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the postacute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

# STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- > The protocol has been published to ensure transparency.
- We searched the Japanese database "Ichushi," which has documented a long history of active resuscitation of the most vulnerable preterm newborns.

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> The review did not include a quality assessment of the included studies.

# INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.<sup>1, 2</sup> In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.<sup>3, 4, 5</sup> Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognized as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the post-acute phase, which can be potentially fatal.<sup>6, 7</sup> Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.<sup>8, 9, 10</sup> However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.<sup>11, 12, 13</sup> Similarly, various echocardiographic findings are used to diagnose PH.<sup>7, 14</sup> Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that

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the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.<sup>15</sup> In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence on the administration of iNO after 7 days of life. It covers initiation criteria as well as dosage, duration, discontinuation criteria, concomitant use of other drugs, and adverse effects.

# METHODS AND ANALYSIS

# **Protocol and registration**

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.<sup>16</sup> This review was conducted in compliance with the published protocol.

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#### **Eligibility criteria**

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, https://doi.org/10.46658/JBIMES-20-12). Articles meeting the following eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as

> randomized controlled trials (RCTs), prospective and retrospective cohort studies, casecontrol studies, and case series. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

# Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO
	after 7 days of age
	Aim to identify the initiation criteria of iNO, postnatal day of the iNO
Concept	initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation
Concept	criteria of iNO therapy, concomitant use of other drugs, and adverse
	effects
	Published between January 2003 and August 2023
	Conducted in developed countries
	Published in English or Japanese
Context	Randomized controlled trial, cohort study, case-control study, and case
	series
	Excluding congenital malformation syndrome and a chromosomal
	abnormality
PCC, Populati	on-Concept-Context; iNO, inhaled nitric oxide
Information	sources

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We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,<sup>17</sup> alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix.

# Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.<sup>18</sup> The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,<sup>19</sup> to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough fulltext review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

# Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 3 and 4).

# Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

# Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results.

# RESULTS

# Selection of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially eligible studies was subsequently performed, leading to the exclusion of an additional 107 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 18 original records were included in this study.

# Characteristics and results of sources of evidence

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.<sup>8,</sup> <sup>9, 11</sup> All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2.

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	Tab	le 2. Summary c	of the findir	igs of the inclu	ded studies		syright
	Author Year	Study design	Country	Setting	Population	Intervention or Concept	in 77 Study findings
Stu	dies investig	ating prophyla	ctic iNO use	e for BPD			
1	Ballard et al. 2006 <sup>8</sup>	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N <sub>2</sub> : n=288	Survival without BPD; 43.9% in NO and 36.8 % in place (RB: 1.23, 95% CI: 1.01–1.51, P=0.042) iNO ground scharged sooner (P=0.04), shorter supplement by oxygen use (P=0.006). There we have boots of prematurity.
2	Ballard et al. 2016 <sup>11</sup>	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Survival with out BPD; 36 weeks, 31.3% vs. 31.7%, RB: 0.98, (95% 61: 0.75–1.28 P=0.89); 40 weeks, 58.7% vs. 54.1%, RB: 2.08, (95% CI: 0.92–1.27 P=0.33). There was no difference in serious adverse events, comorbid these of prematurity, and the severity of lung disease 2.09 weeks.
3	Hasan et al. 2017 <sup>9</sup>	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; respiratory support on 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N <sub>2</sub> : n=175	Surviva without BPD was not improved at 36 weeks. Respiratory and neurodevelopmental outcomes were different at 8–24 months of postmenstrual age. There was no difference in the common complications prematority
Stu	dies investig	ating rescue iN	O use for P	н			ind s
4	Truog et al. 2014 <sup>10</sup>	Retrospectiv e cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at ≥7 days of age	iNO adrainist ration between days 7 and 14 was associated with an increased risk of BPD or death (OR: 2.24, 95% CE 1.23–4.07). No information regarding complications or adverse events of into use was reported.
5	Hsiao et al. 2019 <sup>20</sup>	Retrospectiv e cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5– 2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	Common causes of off-label iNO use included BPD (19/27, 70.2%) and secondary PH (14/27, 51.9%) The Off-label iNO use group demonstrated the poores response and the highest in-hospital mortality (P <0.00
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6	Nakanishi et al. 2023⁴	Retrospectiv e cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acete infants Post-acete neurod Set	O use increased in extremely preterm more severe disease and complications. O was not associated with long-term pmental outcomes at 3 years of age.
7	Oka et al. 2023 <sup>13</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	iNO thraphe There was and responding the Methen participant Early iND 0.89, 952	elated adverse events were not reported. o difference in in-hospital outcomes between and non-responders. binemia (MetHb >5%) did not occur in any s associated with treatment response (OR: 0.7970–0.995, P=0.04)
8	Fraga et al. 2023 <sup>14</sup>	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty (81880 PAH be	patients had echocardiographic evidence of NO, and 19 (56%) after 48 h of iNO (P=0.04). ments were significantly different between before initiation of iNO and after 48–168 h
9	Nakao et al. 2012 <sup>21</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	ک Indicatien; Outcome; D No com	RF with PH (n=10), CLD with PH (n=3) eath (n=8) tions were reported
10	lwatani et al. 2022 <sup>22</sup>	Retrospectiv e cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Backgrowing Indication; G Outcome; D	Histological CAM (n=9), SGA (<-3 SD) (n=2) LD with PH (n=7), HRF with PH (n=5) eath (n=8), HOT (n=3), tracheostomy (n=1)
	iNC	, inhaled nitric o	oxide; GA, {	gestational age;	BW, birth weight; RB, re	lative benefit; CI, c	onfidenceint	rval; OR, odds ratio; BPD,
	bro	nchopulmonary	dysplasia;	RCT, randomize	ed controlled trial; PH, pu	Ilmonary hypertens	sion; HRF, hy	oxic respiratory failure; LVEF,
	left	ventricular eject	tion fractio	on; NRNJ, Neona	atal Research Network of	Japan; IQR, interq	uartile range	PAH; pulmonary artery
	hyp	ertention, CLD; (	chronic lur	ig disease, CAIV	I; chorioamnionitis, SGA;	small for gestation	al age, HOI;	ome oxygen therapy, LVEF; left
	Ven		action, FFI	in, persistent p	fullionary hypertention (			
					12		ograpniq	
				For peer revie	w only - http://bmjopen.bmj.	.com/site/about/guide	lines.xhtml	

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All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),<sup>8</sup> while the remaining studies did not demonstrate improvement.<sup>9, 11</sup> None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.<sup>20</sup>

Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,<sup>4, 10</sup> four retrospective cohort studies conducted in single tertiary centers,<sup>13, 14, 20, 21</sup> and one multicenter retrospective cohort study.<sup>22</sup> Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.<sup>21, 22</sup> The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.<sup>13</sup> noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also found no difference in the incidence of in-hospital outcomes between responders and non-responders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.<sup>4</sup> reported in their retrospective cohort study using the

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Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.<sup>14</sup> emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

#### Synthesis of results

#### Initiation criteria for post-acute iNO

While the diagnostic criteria for PH are often poorly described in the literature, they are essential for the effective and safe administration of iNO in the post-acute phase. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.<sup>8, 9, 11</sup> However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.<sup>12, 13, 14, 20, 22</sup> Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.<sup>12, 13, 14, 22</sup> Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.<sup>14</sup> Accurate diagnosis of nitric-responsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before iNO initiation should be considered a crucial step.

To measure the severity of respiratory compromise, various measures have been utilized. Three studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO<sub>2</sub>]),<sup>8, 11, 12</sup> one utilized the OSI,<sup>13</sup> and two employed the oxygenation index.<sup>12, 21</sup> In out-of-concept studies, Hussein et al. reported the use of

echocardiography for PH diagnosis and noted echocardiographic findings, including

	A summary of t	hese findings is prese	ol.		
	Table 2 Initiatic	an critoria for iNO in c	all of the included studi	or.	
	Author		Initiation criteria	for iNO	
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
5	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO <sub>2</sub> ×100 /SpO <sub>2</sub>	N/A
3	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting	N/A	N/A

			through a PDA. Septal flattening or bowing at end- systole.		
			0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.		
9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	lwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO<sub>2</sub>, partial pressure of oxygen; SpO<sub>2</sub>, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

The starting dose of iNO ranged from 3–20 ppm, with four studies starting at 20 ppm<sup>8, 9, 11, 20</sup>, and one study reporting a maximum dose of 80 ppm.<sup>20</sup> The duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, three RCTs included a 24-day pre-protocol dosing period.<sup>8, 9, 11</sup> Regarding adjunctive medications, reports involving the use of surfactants,<sup>11, 13, 20</sup> inotropes,<sup>12, 20</sup> corticosteroids<sup>13</sup>, bronchodilators<sup>14</sup>, and diuretics<sup>14</sup> were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm <sup>16</sup>

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birth,<sup>8, 9, 11</sup> which aligns with the findings of retrospective studies.<sup>4, 12, 13, 21, 22</sup> However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.<sup>14</sup> The criteria for discontinuation are not well-described. Regarding RCTs <sup>8, 9, 11</sup>, they were designated as protocol treatment. However, for rescue treatment, they probably could not be stopped <sup>13, 14, 20, 21, 22</sup>. Additionally, for retrospective studies <sup>4,10</sup>, it may not be possible to retrieve these data. Hussain implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 h to 59 h; however, the study was excluded from our review because it did not align with the study concept <sup>12</sup>.

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A summary of these data is presented in Table 4.

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Table 4. Summary of the details of post-acute iNO admir	nistration in preterm infants in th	ୁ ଓ e ଭୌପାର୍ଷ ded studies

3 4

34

44 45

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	Discontinuatio	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	ng for uses rei	Specified by the	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant to	Participation of the second se	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	id data mining, Al tra N/A	eur (ABCS)	No differences in common complications of prematurity No elevation in NO <sub>2</sub> or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days: (n=47 or 0.96%)	N/A	N/A	ining, and similar te	open.bmj.com/ on J	N/A
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 1/27 (3.7%) Dopamine 10/27 ; (37.0%) Dobutamine 6/27 (22.2%) Epinephrine 3/27 (11.1%)	A N/A une 9, 2025 at Agence Biblio	N/A
				18		grap	

Page 21	of 29	BMJ Open 69						
1 2 3			N/A			Milrinone 6/27 (22.2%) ,, inc.	2024-08774	
4 5 6 7 8 9	6	Nakanishi et al.	N/A (post-acute iNO; defined as iNO administratio	N/A	26 days [14–70 days]	uding for uses r N/A	N/A	N/A
10 11 12 13 14		2023	n in the late phase of hospitalizatio n)		[11,000035]	elated to text an		
15 16 17	7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant Gar corticosteroid a A	N/A	No complications No methemoglobinemia
18 19 20 21						Bronchodilators; n=16 (43%)		
22 23 24 25 26 27	8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Diuretics; ai Furosemide: n=15 (40%), and Chlorothiazide: si n=16 (43%) ai	N/A	Pulmonary edema; n=1
28 29 30 21	9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	N/A rtechnol	N/A	No complications
32 33 34	10	lwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A	0025 N/A	No methemoglobinemia No jaundice
35 36 37 38		iNO, inhaled nitric oxide					Rip	
39 40 41					liographiq 19			
42 43 44 45	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml							

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# DISCUSSION

# Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of postacute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH.

# Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006<sup>8</sup> demonstrated the effectiveness of post-acute iNO in promoting survival without BPD, while two other studies did not show significant efficacy.<sup>9,</sup> <sup>11</sup> Importantly, large prospective studies reported no adverse events with consistent iNO use.

# Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

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Among these studies, only a few have clearly described the indications for post-acute iNO use,<sup>12, 14</sup> with only three reports utilizing echocardiography as a criterion for diagnosis of PH.<sup>13, 14, 22</sup> However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.<sup>7, 23</sup> Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,<sup>4</sup> may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

#### Other findings

Among the studies mentioned above, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea. Considering the rare reporting of complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

#### Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to 

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> a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. It is essential to promote the use of comprehensive echocardiographic evaluation for PH before administering iNO. While identifying a simple and robust parameter may help streamline the process, it is crucial to consider a holistic approach that encompasses multiple diagnostic criteria to ensure an accurate and effective diagnosis.

# Strengths and limitations

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting

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comprehensive data, including diagnostic criteria for PH before iNO introduction in the postacute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

#### CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of postacute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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#### **CONFLICT OF INTEREST**

None declared.

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# AUTHOR CONTRIBUTIONS

SK and HN conceptualized this study. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial input for the development of the final version. DS and HN provided feedback on the methodology. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) have read and revised the draft, and have approved the final version of the manuscript. SK is responsible for the overall content as guarantor.

# DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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2023;112:358-71.

## **FIGURE LEGEND**

Figure 1: Flow diagram showing the study selection process.





## Supplementary Figure. Search strategy of the scoping review in Pubmed.

Search	Query	Sort By	Filters	Search Details	Results
	Query	SUTL BY	riiters	("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract] OR "preematur*"[Title/Abstract] OR "preeterm*"[Title/Abstract] OR "preeterm*"[Title/Abstract] OR "preeterm*"[Title/Abstract] OR "preeterm*"[Title/Abstract] OR "preeterm*"[Title/Abstract] OR "preeterm*"[Title/Abstract] OR "Preemature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract] OR "Preemature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract] OR "Demature atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "Aerosols"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]] AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract] OR "nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract]] OR "nitric Oxide"[Intle/Abstract] OR "no-inhalation"[Title/Abstract]] AND ("english"[Language] OR "japanese"[Language]] AND	nesuits
7	#4 and #5 and #6	Most Recent		2022/12/01:2023/08/31[Date-Publication]	21
6	("2022/12/01"[Date - Publication] : "2023/08/31"[Date - Publication]) ("english"[Language]) OP	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,989
5	("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,912
4	#1 and #2 and #3	Most Recent	N.	("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "Administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "hale*"[Title/Abstract] OR "No"[Title/Abstract] OR "nasal"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]] AND ("iNO"[Title/Abstract] OR "Nitric Oxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract:~2] OR "nitric	715
3	iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR "Nitric Oxide"[mh] OR "nitric oxide"[tiab:~2] OR "nitric oxides"[tiab:~2] OR "no- inhalation"[tiab]	Most Recent		"iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]	188,676
2	"Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol*[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR inhale*[tiab] OR iNo[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no- inhalation"[tiab]	Most Recent		"administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	336,347
1	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre- term*[tiab] OR "Premature Birth"[mh] OR VLBW[tiab]	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,860

# **BMJ Open**

## Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age Shin Kato<sup>1</sup>, Yohei Minamitani<sup>2</sup>, Miku Hosokawa<sup>3</sup>, Toshinori Nakashima<sup>4</sup>, Sota Iwatani<sup>5</sup>, Katsuya Hirata<sup>6</sup>, Arata Oda<sup>7</sup>, Takushi Hanita<sup>8</sup>, Masafumi Miyata<sup>9</sup>, Fumihiko Namba<sup>2</sup>, Masayuki Ochiai<sup>10</sup>, Atsushi Nakao<sup>3</sup>, Seiji Yoshimoto<sup>5</sup>, Daichi Suzuki<sup>11</sup>, Erika Ota<sup>12</sup>, Hidehiko Nakanishi<sup>13</sup>; on behalf of the Japan Society for Neonatal Health and Development <sup>1</sup> Department of Pediatrics, Japanese Red Cross Aichi Medical Center, Nagoya Daini Hospital, Nagoya, Aichi, Japan <sup>2</sup> Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan <sup>3</sup> Department of Neonatology, Japanese Red Cross Medical Center, Shibuya-ku, Tokyo, Japan <sup>4</sup> Department of Pediatrics, National Hospital Organization Kokura Medical Center, Kitakyushu, Fukuoka, Japan <sup>5</sup> Department of Neonatology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Hyogo, Japan <sup>6</sup>Department of Neonatal Medicine, Osaka Women's and Children's Hospital, Izumi, Osaka, Japan <sup>7</sup>Division of Neonatology, Nagano Children's Hospital, Azumino, Nagano, Japan <sup>8</sup>Center for Perinatal and Neonatal Medicine, Tohoku University Hospital, Sendai, Miyagi, Japan

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## 

## ABSTRACT

**Objectives**: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

**Design**: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

**Data sources**: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

**Eligibility criteria**: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

**Data extraction and synthesis**: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

**Results**: We included 10 reports that analyzed the data from 10 separate studies. The use of iNO therapy was categorized as prophylactic and rescue purpose. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute

phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare. **Conclusion**: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the postacute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- > The protocol has been published to ensure transparency.
- We searched the Japanese database "Ichushi," which has documented a long history of active resuscitation of the most vulnerable preterm newborns.

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> The review did not include a quality assessment of the included studies.

## INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.<sup>1, 2</sup> In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.<sup>3, 4, 5</sup> Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognized as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the post-acute phase, which can be potentially fatal.<sup>6, 7</sup> Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.<sup>8,9, 10</sup> However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.<sup>11, 12, 13</sup> Similarly, various echocardiographic findings are used to diagnose PH.<sup>7, 14</sup> Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that

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the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.<sup>15</sup> In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence on the administration of iNO after 7 days of life. It covers initiation criteria as well as dosage, duration, discontinuation criteria, concomitant use of other drugs, and adverse effects.

## METHODS AND ANALYSIS

#### **Protocol and registration**

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.<sup>16</sup> This review was conducted in compliance with the published protocol.

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## **Eligibility criteria**

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, <u>https://doi.org/10.46658/JBIMES-20-12).</u> We defined the post-acute phase as the late phase of primary hospitalization, i.e. after 7 days of life, based on the definition in previous nationwide surveys by Truog et al.<sup>4</sup> and Nakanishi et al.<sup>6</sup> We employed the 7<sup>th</sup> day of life as the transition point to exclude premature infants suffering from pulmonary hypertension of the newborn. Articles meeting the following

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eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and case series. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

## Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO
ropulation	after 7 days of age
	Aim to identify the initiation criteria of iNO, postnatal day of the iNO
Concept	initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation
	criteria of iNO therapy, concomitant use of other drugs, and adverse
	effects
	Dublished between January 2002 and August 2022
	Published between January 2003 and August 2023
	Conducted in developed countries
Contout	Dublished in English on Innersee
Context	Published in English of Japanese
	Randomized controlled trial, cohort study, case-control study, and case
	series

 Excluding congenital malformation syndrome and a chromosomal abnormality

## PCC, Population-Concept-Context; iNO, inhaled nitric oxide

#### Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,<sup>17</sup> alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix 1.

## Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. (Supplemental Appendix 2)<sup>18</sup> The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,<sup>19</sup> to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough full-text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

## 

## Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 2 to 4).

## Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

## Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results. iles

## RESULTS

## Selection and characteristics of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially eligible studies was subsequently performed, leading to the exclusion of an additional 117 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 10 original records were included in this study. The findings of these included studies are summarized in Table 2.

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	Table 2. S	ummary of the	findings of	the included st	udies		-087740 . ht, inclu
	Author Year	Study design	Country	Setting	Population	Intervention or Concept	Study findings
Stu	dies investig	ating prophyla	ctic iNO use	e for BPD			- use
1	Ballard et al. 2006 <sup>8</sup>	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N <sub>2</sub> : n=288	Surviva 🗸 🏭 and the provided and the p
2	Ballard et al. 2016 <sup>11</sup>	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Surviva员遭遇的ut BPD; 36 weeks, 31.3% vs. 31.7%, RB 0.98, (99% 图: 0.75–1.28 P=0.89); 40 weeks, 58.7% vs 54.1%, 图 3.08, (95% CI: 0.92–1.27 P=0.33). There 如何 o difference in serious adverse events, comorbanties of prematurity, and the severity of lung disease to 36 weeks.
3	Hasan et al. 2017 <sup>9</sup>	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; respiratory support on 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N <sub>2</sub> : n=175	Surviva without BPD was not improved at 36 weeks. Respiratory and neurodevelopmental outcomes were different at 18–24 months of postmenstrual age. There was to difference in the common complication prematerity.
Stu	dies investig	ating rescue iN	O use for P	Ή			simil <sup>on</sup>
4	Truog et al. 2014 <sup>10</sup>	Retrospectiv e cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at 7 days of age	iNO adminigtration between days 7 and 14 was associated with an increased risk of BPD or death (OF 2.24, 955%CF 1.23–4.07). No information regarding complications or adverse events of into use was reported.
5	Hsiao et al. 2019 <sup>20</sup>	Retrospectiv e cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5– 2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	نة Common causes of off-label iNO use included BPD (19/27, 70.5%) and secondary PH (14/27, 51.9%) The Off-labgel iNO use group demonstrated the poore response and the highest in-hospital mortality (P <0.0
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6	Nakanishi et al. 2023 <sup>4</sup>	Retrospectiv e cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acete encoder infants withom Post-acete encoder infants withom Post-acete encoder neurod	D use increased in extremely preterm ore severe disease and complications. D was not associated with long-term mental outcomes at 3 years of age.
7	Oka et al. 2023 <sup>13</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	iNO thrang fel There was son respondension Methem Of Bo participant Early iND was 0.89, 95% et al.	ated adverse events were not reported. difference in in-hospital outcomes betwe d non-responders. inemia (MetHb >5%) did not occur in any associated with treatment response (OR: 0.7970–0.995, P=0.04)
8	Fraga et al. 2023 <sup>14</sup>	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty (81%) PAH bebyer FiO <sub>2</sub> requirement time points be (P=0.05	atients had echocardiographic evidence O, and 19 (56%) after 48 h of iNO (P=0.04 ents were significantly different betweer efore initiation of iNO and after 48–168 h
9	Nakao et al. 2012 <sup>21</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	Indicatian; BRI Outcome; Bea No complication	F with PH (n=10), CLD with PH (n=3) th (n=8) ons were reported
10	lwatani et al. 2022 <sup>22</sup>	Retrospectiv e cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Backgrowing H Indicatien; ELL Outcome; Eac	listological CAM (n=9), SGA (<-3 SD) (n=2 D with PH (n=7), HRF with PH (n=5) th (n=8), HOT (n=3), tracheostomy (n=1)
	iNO, inha bronchop ventricula chronic lu PPHN; pe	led nitric oxide; oulmonary dyspla ar ejection fractio ing disease, CAM rsistent pulmona	GA, gestat asia; RCT, i on; NRNJ, 1; chorioar ary hypert	ional age; BW, randomized cor Neonatal Resea mnionitis, SGA; ension of the ne	birth weight; RB, relative trolled trial; PH, pulmon rch Network of Japan; IC small for gestational age wborn, MV; mechanical	benefit; CI, confide ary hypertension; H R, interquartile ran , HOT; home oxyget ventilation	ence intereal; OF IRF, hypogic es Ige; PAH; pultho n therapy, LV F;	R, odds ratio; BPD, piratory failure; LVEF, left nary artery hypertension, CLD; left ventricle ejection fraction,
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## Synthesis of results

## Initiation criteria for post-acute iNO

The initiation criteria for post-acute iNO are poorly described in the literature; one of the most critical initiation criteria is echocardiographic diagnosis of PH, since NO acts specifically on pulmonary smooth muscle cells to decrease their tone, thus reducing pulmonary blood pressure. While the diagnostic criteria for PH are often poorly described in the literature, they are essential for the effective and safe administration of iNO in the post-acute phase. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.<sup>8, 9, 11</sup> However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.<sup>12, 13, 14, 20, 22</sup> Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.<sup>12,</sup> <sup>13, 14, 22</sup> Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.<sup>14</sup> Accurate diagnosis of nitricresponsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before iNO initiation, as well as other multiple diagnostic criteria, should be considered crucial for the accurate and effective diagnosis of PH.

To measure the severity of respiratory compromise, various measures have been utilized. Three studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO<sub>2</sub>]),<sup>8, 11, 12</sup> one utilized the OSI,<sup>13</sup> and two employed the oxygenation index.<sup>12, 21</sup> In out-of-concept studies, Hussein et al. reported the use of

echocardiography for PH diagnosis and noted echocardiographic findings, including

flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the

PFO/PDA level.<sup>12</sup> They also reported a 60% reduction in iNO use following the

implementation of a weaning protocol.

A summary of these findings is presented in Table 3.

## Table 3. Initiation criteria for iNO in all of the included studies

	Author		Initiation criteria	for iNO	
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO <sub>2</sub> ×100 /SpO <sub>2</sub>	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting	N/A	N/A
			14		

			through a PDA. Septal flattening or bowing at end- systole.		
			0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.		
9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	Iwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO<sub>2</sub>, partial pressure of oxygen; SpO<sub>2</sub>, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

This section summarizes details of the post-acute iNO administration as outlined in the PCC framework, such as postnatal day of iNO initiation, dosage of iNO, duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects. The initiation day and duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, three RCTs included a 24-day pre-protocol dosing period.<sup>8, 9, 11</sup> The criteria for discontinuation are not well-described. Regarding RCTs,<sup>8, 9, 11</sup> they were designated as protocol treatment. However, for rescue treatment, they

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probably could not be stopped.<sup>13, 14, 20, 21, 22</sup> Additionally, for retrospective studies,<sup>4,10</sup> it may not be possible to retrieve these data. Hussain implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 h to 59 h; however, the study was excluded from our review because it did not align with the study concept.<sup>12</sup> The starting dose of iNO ranged from 3 to 20 ppm, with four studies starting at 20 ppm<sup>8, 9, 11,</sup> <sup>20</sup> and one study reporting a maximum dose of 80 ppm.<sup>20</sup> Regarding adjunctive medications, reports involving the use of surfactants,<sup>11, 13, 20</sup> inotropes,<sup>12, 20</sup> corticosteroids,<sup>13</sup> bronchodilators,<sup>14</sup> and diuretics<sup>14</sup> were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm birth,<sup>8, 9, 11</sup> which aligns with the findings of retrospective studies.<sup>4, 12, 13, 21, 22</sup> However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.<sup>14</sup> A summary of these data is presented in Table 4.

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	∰ Discontinuatio <sup>4</sup> n criteria 9	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	ng for uses re	Specified by the	No difference in the complications of prematurity No methemoglobinemi
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant 6	protocol	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	N/A N/A	becified by the protocol	No differences in common complications of prematurity No elevation in NO <sub>2</sub> or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days: (n=47 or 0.96%)	N/A	N/A	N/A N/A	omjopen.bmj.com/ o	N/A
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 1/27 (3.7%) Dopamine 10/27 (37.0%) Dobutamine 6/27 (22.2%) Epinephrine 3/27 (11.1%) Milrinone 6/27 (22.2%)	on June 9, 2025 at Agence Bib	N/A
				17		liographi	

				BMJ Open	by сор	ijopen-2	Page
6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administratio n in the late phase of hospitalizatio n)	N/A	26 days [14–70 days]	vright, including for uses related N/A	024-087740 on 30 December 203 Enceimen	N/A
7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant corticosteroid	14. N/A Super	No complications No methemoglobinemia
8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Bronchodilators; n=16 (43%) Diuretics; Furosemide: n=15 (40%), Chlorothiazide: n= n=16 (43%)	A N/A sd from http://bmjopen.br	Pulmonary edema; n=1
9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	N/A similar	nj.com/ N/A	No complications
10	lwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A N/A	June 9, 20	No methemoglobinemi No jaundice
	iNO, inhale	ed nitric oxide			Ğ	25 at Agence Biblic	
				18		ographiqu	
			For peer review only - http://	bmjopen.bmj.com/site,	/about/guidelines.xhtml	e de l	

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Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.<sup>8,</sup> <sup>9, 11</sup> All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2. All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),<sup>8</sup> while the remaining studies did not demonstrate improvement.<sup>9, 11</sup> None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.<sup>20</sup>

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Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,<sup>4, 10</sup> four retrospective cohort studies conducted in single tertiary centers,<sup>13, 14, 20, 21</sup> and one multicenter retrospective cohort study.<sup>22</sup> Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.<sup>21, 22</sup> The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.<sup>13</sup> noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also

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> found no difference in the incidence of in-hospital outcomes between responders and nonresponders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.<sup>4</sup> reported in their retrospective cohort study using the Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.<sup>14</sup> emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

## DISCUSSION

## Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of postacute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH.

## Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006<sup>8</sup> demonstrated the effectiveness of post-acute iNO in

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promoting survival without BPD, while two other studies did not show significant efficacy.<sup>9,</sup> <sup>11</sup> Importantly, large prospective studies reported no adverse events with consistent iNO use.

## Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,<sup>12, 14</sup> with only three reports utilizing echocardiography as a criterion for diagnosis of PH.<sup>13, 14, 22</sup> However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.<sup>7, 23</sup> Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

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Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,<sup>4</sup> may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

## **Other findings**

Among the studies mentioned above, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea. Considering the rare reporting of 21

complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

#### Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. It is essential to promote the use of comprehensive echocardiographic evaluation for PH before administering iNO. While identifying a simple and robust parameter may help streamline the process, it is crucial to consider a holistic approach that encompasses multiple diagnostic criteria to ensure an accurate and effective diagnosis.

#### **Strengths and limitations**

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD 22

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alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the postacute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

#### CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of postacute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

## 

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## **CONFLICT OF INTEREST**

None declared.

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## AUTHOR CONTRIBUTIONS

SK and HN conceptualized this study. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial input for the development of the final version. DS and HN provided feedback on the methodology. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and

HN) have read and revised the draft, and have approved the final version of the manuscript.

SK is responsible for the overall content as a guarantor.

## **DATA SHARING STATEMENT**

All data relevant to the study are included in the article or uploaded as supplementary

information.

## PATIENT CONSENT FOR PUBLICATION

Not applicable.

## **ETHICS APPROVAL**

Obtaining an institutional review board approval is not required because of the nature of

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the methodology used in the analysis.

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## **FIGURE LEGEND**

Figure 1: Flow diagram showing the study selection process.

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## Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and opper sources



## Supplementary Appendix 1. Search strategy of the scoping review in Pubmed.

number	Query	Sort By	Filters	Search Details	Results
				("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract] OR "reonatal under weight"[Title/Abstract] OR "prematur*"[Title/Abstract] OR "preterm *"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm *"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm *"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm *"[Title/Abstract] OR "premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]] AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxides"[Title/Abstract] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Titl	
7	7 #4 and #5 and #6	Most Recent		2022/12/01:2023/08/31[Date - Publication]	
e	5 "2023/08/31"[Date - Publication])	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,9
5	("english"[Language]) OR 5 ("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,9
	1 #1 and #2 and #3	Most Recent		Terms] OR "infant, premature, diseases" [MeSH Terms] OR "infant, premature [inesh" Terms] OR "infant, premature, diseases" [MeSH Terms] OR "iow "LBW" [Title/Abstract] OR "low birth weight*" [Title/Abstract] OR "low birthweight*" [Title/Abstract] OR "neonatal underweight" [Title/Abstract:~3] OR "neonatal under weight" [Title/Abstract:~3] OR "prematur*" [Title/Abstract] OR "preterm*" [Title/Abstract] OR "pre matur*" [Title/Abstract] OR "preterm*" [Title/Abstract] OR "Premature Birth" [MeSH Terms] OR "VLBW" [Title/Abstract]) AND ("administration, inhalation" [MeSH Terms] OR "aerosol*" [Title/Abstract] OR "Aerosols" [MeSH Terms] OR "aerosol*" [Title/Abstract] OR "atomizer*" [Title/Abstract] OR "inhala*" [Title/Abstract] OR "inhale*" [Title/Abstract] OR "inhala*" [Title/Abstract] OR "inhale*" [Title/Abstract] OR "Nebulizers and Vaporizers" [MeSH Terms] OR "Respiratory Tract Absorption" [MeSH Terms] OR "vaporizer*" [Title/Abstract] OR "no-inhalation" [Title/Abstract:~2] OR "Nitric Oxide" [MeSH Terms] OR "Nitric Oxide" [Title/Abstract:~2] OR "Nitric Oxide" [MeSH Terms] OR "Nitric Oxide" [Title/Abstract:~2] OR "nitric Oxide" [MeSH Terms] OR "no-inhalation" [Title/Abstract:~2] OR "Nitric Oxide" [MeSH Terms] OR "Nitric Oxide" [Title/Abstract:~2] OR "Nitric Oxide" [MeSH Terms] OR "no-inhalation" [Title/Abst	
	iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR	Most Recent			,
3	"Nitric Oxide"[mh] OR "nitric oxide"[tiab:~2] OR "nitric oxides"[tiab:~2] OR "no- 3 inhalation"[tiab]	Most Recent		"iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]	188,6
2	"Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol*[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR Inhale*[tiab] OR INO[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no- 2 inhalation"[tiab]	Most Recent		"administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	336,3
	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre- term*[tiab] OR "Premature Birth"[mh] OR	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,
# **BMJ Open**

# Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age Shin Kato<sup>1</sup>, Yohei Minamitani<sup>2</sup>, Miku Hosokawa<sup>3</sup>, Toshinori Nakashima<sup>4</sup>, Sota Iwatani<sup>5</sup>, Katsuya Hirata<sup>6</sup>, Arata Oda<sup>7</sup>, Takushi Hanita<sup>8</sup>, Masafumi Miyata<sup>9</sup>, Fumihiko Namba<sup>2</sup>, Masayuki Ochiai<sup>10</sup>, Atsushi Nakao<sup>3</sup>, Seiji Yoshimoto<sup>5</sup>, Daichi Suzuki<sup>11</sup>, Erika Ota<sup>12</sup>, Hidehiko Nakanishi<sup>13</sup>; on behalf of the Japan Society for Neonatal Health and Development <sup>1</sup> Department of Pediatrics, Japanese Red Cross Aichi Medical Center, Nagoya Daini Hospital, Nagoya, Aichi, Japan <sup>2</sup> Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan <sup>3</sup> Department of Neonatology, Japanese Red Cross Medical Center, Shibuya-ku, Tokyo, Japan <sup>4</sup> Department of Pediatrics, National Hospital Organization Kokura Medical Center, Kitakyushu, Fukuoka, Japan <sup>5</sup> Department of Neonatology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Hyogo, Japan <sup>6</sup>Department of Neonatal Medicine, Osaka Women's and Children's Hospital, Izumi, Osaka, Japan <sup>7</sup>Division of Neonatology, Nagano Children's Hospital, Azumino, Nagano, Japan <sup>8</sup>Center for Perinatal and Neonatal Medicine, Tohoku University Hospital, Sendai, Miyagi, Japan

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# ABSTRACT

**Objectives**: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

**Design**: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

**Data sources**: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

**Eligibility criteria**: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

**Data extraction and synthesis**: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

**Results**: We included 10 reports that analyzed the data from 10 separate studies. The use of iNO therapy was categorized as prophylactic and rescue purpose. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute

phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare. **Conclusion**: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the postacute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- > The protocol has been published to ensure transparency.
- We searched the Japanese database "Ichushi," which has documented a long history of active resuscitation of the most vulnerable preterm newborns.

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> The review did not include a quality assessment of the included studies.

## INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.<sup>1, 2</sup> In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.<sup>3, 4, 5</sup> Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognized as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the post-acute phase, which can be potentially fatal.<sup>6, 7</sup> Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.<sup>8, 9, 10</sup> However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.<sup>11, 12, 13</sup> Similarly, various echocardiographic findings are used to diagnose PH.<sup>7, 14</sup> Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that

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the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.<sup>15</sup> In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence on the administration of iNO after 7 days of life. It covers initiation criteria as well as dosage, duration, discontinuation criteria, concomitant use of other drugs, and adverse effects.

## METHODS AND ANALYSIS

#### **Protocol and registration**

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.<sup>16</sup> This review was conducted in compliance with the published protocol.

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## **Eligibility criteria**

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, <u>https://doi.org/10.46658/JBIMES-20-12).</u> We defined the post-acute phase as the late phase of primary hospitalization, i.e. after 7 days of life, based on the definition in previous nationwide surveys by Truog et al.<sup>4</sup> and Nakanishi et al.<sup>6</sup> We employed the 7<sup>th</sup> day of life as the transition point to exclude premature infants suffering from pulmonary hypertension of the newborn. Articles meeting the following

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eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and case series. We recruited preterm infants born at < 34 weeks of gestation because we have focused on pulmonary hypertension in the post-acute phase in newborns, a complication primarily observed in extremely preterm infants. To maintain the focus of our review, we narrowed our inclusion criteria by excluding the late preterm infants born between 34 to 36 weeks of gestation, as they rarely develop PH in their post-acute phase. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

# Table 1. PCC framework of this scoping review

	Preterm infants born at <34 weeks of gestation and treated with iNO
Population	after 7 days of age
	Aim to identify the initiation criteria of iNO, postnatal day of the iNO
Concept	initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation
	criteria of iNO therapy, concomitant use of other drugs, and adverse
	effects

	Published between January 2003 and August 2023
	Conducted in developed countries
	Published in English or Japanese
Context	Randomized controlled trial, cohort study, case-control study, and case
	series
	Excluding congenital malformation syndrome and a chromosomal
	abnormality
PCC, Populat	ion-Concept-Context; iNO, inhaled nitric oxide

## Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,<sup>17</sup> alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix 1.

# Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. (Supplemental Appendix 2)<sup>18</sup> The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,<sup>19</sup> to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough full-text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

## Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 2 to 4).

#### Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

## Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results.

## RESULTS

#### Selection and characteristics of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially 10

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 eligible studies was subsequently performed, leading to the exclusion of an additional 117 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 10 original records were included in this study. The findings of these included studies are summarized in Table 2.

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	Table 2. S	ummary of the	findings of	the included st	udies		37740 c	
	Author Year	Study design	Country	Setting	Population	Intervention or Concept	ାମ୍ମିକ କ୍ଷି ସ୍ଥ୍ୟ କ୍ଷି Study finding: ବିସ	5
Stud	dies investig	ating prophyla	ctic iNO use	e for BPD			use use	
1	Ballard et al. 2006 <sup>8</sup>	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N <sub>2</sub> : n=288	Surviva 🖓 🛱 bout BPD; 43.9% in NO a (RB: 1.2%) % CI: 1.01–1.51, P=0.04 iNO groget k scharged sooner (P=0.06) supplemental oxygen use (P=0.006) There were booshort-term safety co difference is the complications of p	and 36.8 % in place 42) 04), shorter 1. ncerns and no rematurity.
2	Ballard et al. 2016 <sup>11</sup>	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Surviva and the second	3% vs. 31.7%, RB: ) weeks, 58.7% vs. P=0.33). adverse events, he severity of lung
3	Hasan et al. 2017 <sup>9</sup>	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; respiratory support on 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N <sub>2</sub> : n=175	Surviva without BPD was not improved the service of	oved at 36 weeks. al outcomes were enstrual age. mon complications
Stuc	dies investig	ating rescue iN	O use for P	H			simil.	
4	Truog et al. 2014 <sup>10</sup>	Retrospectiv e cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at 7 days of age	iNO adminigtration between days 7 associated with an increased risk of 2.24, 95%CF 1.23–4.07). No information regarding complicat events of into use was reported.	and 14 was BPD or death (OR: tions or adverse
5	Hsiao et al. 2019 <sup>20</sup>	Retrospectiv e cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5– 2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	بة نق Common causes of off-label iNO use (19/27, 70.ع) and secondary PH (1 The Off-labgil iNO use group demon response and the highest in-hospita	e included BPD .4/27, 51.9%) strated the poores Il mortality (P <0.00
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6	Nakanishi et al. 2023 <sup>4</sup>	Retrospectiv e cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acete evere disease and complications. Post-acete evere disease and complications. Post-acete evere disease and complications. Post-acete evere disease and complications.
7	Oka et al. 2023 <sup>13</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	iNO thr way elated adverse events were not reported. There way is odifference in in-hospital outcomes between responders. Methem of Bbinemia (MetHb >5%) did not occur in any participation in the second with treatment response (OR: 0.89, 95% (G: 0.7970–0.995, P=0.04)
8	Fraga et al. 2023 <sup>14</sup>	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty ( $\vec{a}_1$ ) and $\vec{b}_2$ patients had echocardiographic evidence of PAH be $\vec{b}_2$ PAH
9	Nakao et al. 2012 <sup>21</sup>	Retrospectiv e cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	غَّةُ الْعَوْمَ Indicatian; BRF with PH (n=10), CLD with PH (n=3) Outcomy; Breath (n=8) No complications were reported
10	lwatani et al. 2022 <sup>22</sup>	Retrospectiv e cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Background Histological CAM (n=9), SGA (<-3 SD) (n=2) Indication (LD with PH (n=7), HRF with PH (n=5) Outcome: Geath (n=8), HOT (n=3), tracheostomy (n=1)
	iNO, inha bronchop ventricula chronic lu PPHN; pe	led nitric oxide; oulmonary dyspla ar ejection fraction ing disease, CAN rsistent pulmon	GA, gestat asia; RCT, r on; NRNJ, I A; chorioar ary hyperto	onal age; BW, I andomized con Neonatal Resea nnionitis, SGA; ension of the ne	pirth weight; RB, relative strolled trial; PH, pulmon rch Network of Japan; IQ small for gestational age, ewborn, MV; mechanical	benefit; CI, confide ary hypertension; H R, interquartile ran HOT; home oxyger ventilation	ence intergal; OR, odds ratio; BPD, IRF, hypogic espiratory failure; LVEF, left age; PAH; pulthonary artery hypertension, CLD; n therapy, LV F; left ventricle ejection fraction,
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## Synthesis of results

# Initiation criteria for post-acute iNO

The initiation criteria for post-acute iNO are poorly described in the literature; one of the most critical initiation criteria is echocardiographic diagnosis of PH, since NO acts specifically on pulmonary smooth muscle cells to decrease their tone, thus reducing pulmonary blood pressure. While the diagnostic criteria for PH are often poorly described in the literature, they are essential for the effective and safe administration of iNO in the post-acute phase. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.<sup>8, 9, 11</sup> However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.<sup>12, 13, 14, 20, 22</sup> Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.<sup>12,</sup> <sup>13, 14, 22</sup> Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.<sup>14</sup> Accurate diagnosis of nitricresponsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before iNO initiation, as well as other multiple diagnostic criteria, should be considered crucial for the accurate and effective diagnosis of PH.

To measure the severity of respiratory compromise, various measures have been utilized. Three studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO<sub>2</sub>]),<sup>8, 11, 12</sup> one utilized the OSI,<sup>13</sup> and two employed the oxygenation index.<sup>12, 21</sup> In out-of-concept studies, Hussein et al. reported the use of

echocardiography for PH diagnosis and noted echocardiographic findings, including flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the

PFO/PDA level.<sup>12</sup> They also reported a 60% reduction in iNO use following the

implementation of a weaning protocol.

A summary of these findings is presented in Table 3.

# Table 3. Initiation criteria for iNO in all of the included studies

	Author		Initiation criteria	for iNO	
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO <sub>2</sub>	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO <sub>2</sub> ×100 /SpO <sub>2</sub>	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting	N/A	N/A
			15		

dosing period.<sup>8, 9, 11</sup> The criteria for discontinuation are not well-described. Regarding RCTs,<sup>8,</sup>

through a PDA.

Septal flattening or

			bowing at end- systole. TPV:RVET ratio, 0.2– 0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.		
9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	Iwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO<sub>2</sub>, partial pressure of oxygen;  $SpO_2$ , peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

This section summarizes details of the post-acute iNO administration as outlined in the PCC framework, such as postnatal day of iNO initiation, dosage of iNO, duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects. The initiation day and duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, three RCTs included a 24-day pre-protocol <sup>9, 11</sup> they were designated as protocol treatment. However, for rescue treatment, they

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probably could not be stopped.<sup>13, 14, 20, 21, 22</sup> Additionally, for retrospective studies,<sup>4,10</sup> it may not be possible to retrieve these data. Hussain implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 h to 59 h; however, the study was excluded from our review because it did not align with the study concept.<sup>12</sup> The starting dose of iNO ranged from 3 to 20 ppm, with four studies starting at 20 ppm<sup>8, 9, 11,</sup> <sup>20</sup> and one study reporting a maximum dose of 80 ppm.<sup>20</sup> Regarding adjunctive medications, reports involving the use of surfactants,<sup>11, 13, 20</sup> inotropes,<sup>12, 20</sup> corticosteroids,<sup>13</sup> bronchodilators,<sup>14</sup> and diuretics<sup>14</sup> were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm birth,<sup>8, 9, 11</sup> which aligns with the findings of retrospective studies.<sup>4, 12, 13, 21, 22</sup> However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.<sup>14</sup> A summary of these data is presented in Table 4.

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Table 4. Summary of the details of post-acute iNO administration in preterm infants in the	id c	luded studies

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	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	a Discontinuatio 4 n criteria	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	ng for uses re N/A	Specified by the	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant o	protocol Support	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	nd data mining, A N/A	Affective Affective	No differences in common complications of prematurity No elevation in NO <sub>2</sub> or methemoglobin level
1	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days: (n=47 or 0.96%)	N/A	N/A	N/A N/A	bmjopen.bmj.com/	N/A
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 1/27 (3.7%) Dopamine 10/27 (37.0%) Dobutamine 6/27 (22.2%) Epinephrine 3/27 (11.1%) Milrinone 6/27 (22.2%)	'on June 9, 2025 at Agence Bib	N/A
				18		liographic	
			For peer review only - http://bmj	open.bmj.com/site,	/about/guidelines.xhtml	lue de l	

Page 21 of	31				BMJ Open	1 by cop		
1 2 3 4 5 6 7 8 9 10	6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administratio n in the late phase of hospitalizatio n)	N/A	26 days [14–70 days]	024-087740 on 30 December 20; Enseignen yright, including for uses relate N/A N/A	N/A	N/A
11 12 13 14	7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant to the Surfactant to the Surfactant to the Superior	N/A	No complications No methemoglobinemia
15 16 17 18 19 20 21 22 23 24	8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Bronchodilators; aded from http://bmjopen.bu Bronchodilators; data mining, Diuretics; Furosemide: n=15 (40%), Chlorothiazide: n=16 (43%) n=16 (43%)	N/A	Pulmonary edema; n=1
25 26 27 28	9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	nd similar N/A	N/A	No complications
29 30 31	10	lwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A N/A	N/A	No methemoglobinemia No jaundice
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46		iNO, inhale	ed nitric oxide	For peer review only - http://b	19 omjopen.bmj.com/site	ies. S. Bibliographique de I /about/guidelines.xhtml		

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.<sup>8,</sup> <sup>9, 11</sup> All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2. All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),<sup>8</sup> while the remaining studies did not demonstrate improvement.<sup>9, 11</sup> None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.<sup>20</sup>

Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,<sup>4, 10</sup> four retrospective cohort studies conducted in single tertiary centers,<sup>13, 14, 20, 21</sup> and one multicenter retrospective cohort study.<sup>22</sup> Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.<sup>21, 22</sup> The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.<sup>13</sup> noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also

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found no difference in the incidence of in-hospital outcomes between responders and nonresponders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.<sup>4</sup> reported in their retrospective cohort study using the Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.<sup>14</sup> emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

## DISCUSSION

## Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of postacute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

## Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006<sup>8</sup> demonstrated the effectiveness of post-acute iNO in

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promoting survival without BPD, while two other studies did not show significant efficacy.<sup>9,</sup> <sup>11</sup> Importantly, large prospective studies reported no adverse events with consistent iNO use.

## Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,<sup>12, 14</sup> with only three reports utilizing echocardiography as a criterion for diagnosis of PH.<sup>13, 14, 22</sup> However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.<sup>7, 23</sup> Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,<sup>4</sup> may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

## **Other findings**

Among the studies mentioned above, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea. Considering the rare reporting of 22

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complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

#### Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. It is essential to promote the use of comprehensive echocardiographic evaluation for PH before administering iNO. While identifying a simple and robust parameter may help streamline the process, it is crucial to consider a holistic approach that encompasses multiple diagnostic criteria to ensure an accurate and effective diagnosis.

#### **Strengths and limitations**

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD 23

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alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the postacute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

## CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of post-

acute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

#### ACKNOWLEDGMENTS

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# **CONFLICT OF INTEREST**

None declared.

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# **AUTHOR CONTRIBUTIONS**

SK and HN conceptualized this study. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial 25

> input for the development of the final version. DS and HN provided feedback on the methodology. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) have read and revised the draft, and have approved the final version of the manuscript. SK is responsible for the overall content as a guarantor.

# DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary

information.

## PATIENT CONSENT FOR PUBLICATION

Not applicable.

## **ETHICS APPROVAL**

Obtaining an institutional review board approval is not required because of the nature of

the methodology used in the analysis.

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## **FIGURE LEGEND**

Figure 1: Flow diagram showing the study selection process.

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# Supplementary Appendix 1. Search strategy of the scoping review in Pubmed.

5	Search	Queru	Sort By	Filtors	Sourch Dataile	Populto
	number	Query	зон ву	FILLEIS	Search Details	Results
0 1 2 3 4 5 6 7 8 9 0 1					("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "INO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]] AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric	
2					oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]) AND ("english"[Language] OR "iananese"[Language]) AND	
3	7	#4 and #5 and #6	Most Recent		2022/12/01:2023/08/31[Date - Publication]	21
4		("2022/12/01"[Date - Publication] :				
5	6	"2023/08/31"[Date - Publication])	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,989
6	5	("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,912
.7 .8 .9 .0 .1 .2 .3 .4 .5 .6 .7 .8 .9 .0 .1 .5 .6 .7 .8 .9 .0 .1 .2 .3 .4 .5 .6 .7 .8 .9 .0 .1 .2 .3 .4 .5 .60 .1 .1 .2 .3 .4 .5 .60 .1 .1 .2 .3 .4 .5 .60 .5 .4 .5 .60 .5 .4 .5 .60 .5 .5 .60 .5 .7 .5 .60 .5 .7 .5 .60 .5 .5 .5 .5 .5 .5 .5 .5 .5 .5 .5 .5 .5	4	#1 and #2 and #3	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "ncbulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]] AND ("iNO"[Title/Abstract] OR "Nitric Oxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract:~2] OR "nitric	715
3		iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR			"iNO"[Title/Abstract] OP "Nitrogan Manavide"[Title/Abstract:2] OP "Nitric	
4		OR "nitric oxides"[tiab:~2] OR "no-			Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric	
5 6 7 8 9 0 1 2 3	2	inhalation"[tiab] "Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol *[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR inhale*[tiab] OR iNO[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no- inhalation"[tiab]	Most Recent		oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract] "administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	188,676 336,347
4 5 6 7 8 9 0	1	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre- term*[tiab] OR "Premature Birth"[mh] OR VLBW[tiab]	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,860