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Epidemiologic evaluation of inhaled nitric oxide use among neonates with gestational age less than 35 weeks

Allison M. Peluso MD[1] | Hasan F. Othman MD[2] | Sreenivas Karnati MD[1] | Ibrahim Sammour MD[1] | Hany Z. Aly MD[1]

[1]Department of Neonatology, Cleveland Clinic Children's Hospital, Cleveland, Ohio, USA

[2]Department of Pediatrics, Michigan State University/Sparrow Health System, Lansing, Michigan, USA

Correspondence
Allison M. Peluso, MD, Department of Neonatology, Cleveland Clinic Children's Hospital, Cleveland, OH 44195, USA.
Email: pelusoa@ccf.org

Abstract

Background and Objectives: The use of inhaled nitric oxide (iNO) in +late preterm and term infants with pulmonary hypertension is Food and Drug Administration (FDA) approved and has improved outcomes and survival. iNO use is not FDA approved for preterm infants and previous studies show no mortality benefit. The objectives were 1) to determine the usage of iNO among preterm neonates <35 weeks before and after the 2010 National Institutes of Health consensus statement and 2) to evaluate characteristics and outcomes among preterm neonates who received iNO.

Methods: This is a population-based cross-sectional study. Billing and procedure codes were used to determine iNO usage. Data were queried from the National Inpatient Sample from 2004 to 2016. Neonates were included if gestational age was <35 weeks. The epochs were spilt into 2004–2010 (Epoch 1) and 2011–2016 (Epoch 2). Prevalence of iNO use, mortality, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, length of stay, mechanical ventilation, and cost of hospitalization.

Results: There were 4865 preterm neonates <35 weeks who received iNO. There was a significant increase in iNO use during Epoch 2 ($p < 0.001$). There was significantly higher use in Epoch 2 among neonates small for gestational age (SGA) 2.3% versus 7.2%, congenital heart disease (CHD) 11.1% versus 18.6%, and BPD 35.2% versus 46.8%. Mortality was significantly lower in Epoch 2 19.8% versus 22.7%.

Conclusion: Usage of iNO was higher after the release of the consensus statement. The increased use of iNO among preterm neonates may be targeted at specific high-risk populations such as SGA and CHD neonates. There was lower mortality in Epoch 2; however, the cost was doubled.

KEYWORDS

health services, hypoxic respiratory failure, prematurity, pulmonary hypertension

Abbreviations: FDA, Food and Drug Administration; HCUP, Healthcare Cost and Utilization Project; ICD-9, International Classification of Diseases, ninth revision; iNO, inhaled nitric oxide; LOS, length of stay; NIH, National Institutes of Health; NIS, National Inpatient Sample; SGA, small for gestational age.

This study was presented at the Pediatric Academic Society meeting on May 4, 2021.

1 | INTRODUCTION

Inhaled nitric oxide (iNO) is Food and Drug Administration (FDA) approved for use in neonates with a gestational age of 35 weeks and greater with hypoxic respiratory failure due to pulmonary hypertension. The use in this population has led to a substantial reduction in mortality and extracorporal membrane oxygen use.[1–6]

Pulmonary hypertension exists in the preterm neonate and can be responsive to iNO. However, in preterm neonates, the evidence has not shown significant improvements in mortality,[7–23] chronic lung disease,[8,15,17–19,22–25] retinopathy of prematurity,[19,26] reduction in cerebral palsy,[8,12,15,24] reduction in neurodevelopmental delays,[8–10,12,15,18,24,27] or long term pulmonary function.[28] In 2010, the National Institutes of Health (NIH)[29] published an expert consensus statement regarding the use of iNO in preterm neonates which recommended cautious use. There are potential adverse effects of iNO and these effects are greater as gestational age decreases. There is also a known significant cost to the use of iNO.[4,11,30] A previous evaluation of the use of iNO among neonates <35 weeks indicates continued use without significant improvement in outcomes.[8]

To date, there is no comprehensive national evaluation of the use of iNO among neonates <35 weeks since the release of the consensus statement. The objectives of this study were to determine the prevalence of iNO among preterm neonates <35 weeks over time as well as in respect to the 2010 NIH consensus statement; to evaluate characteristics and outcomes among preterm neonates who used iNO.

2 | MATERIALS AND METHODS

The study population was queried from the National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project[31] (HCUP). The NIS database, released annually, is composed of a random sample of 20% of the discharges from participating hospitals in 47 states in the USA. The study did not require Institutional Review Board (IRB) review because the database is a limited dataset and under Health Insurance Portability and Accountability Act review, IRB is not required (data use agreement training, Section 8. https://www.hcup-us.ahrq.gov/DUA/dua_508/DUA508version.jsp#hipaa). The study population criteria included infants admitted at ≤28 days of life with a gestational age less than 35 weeks between 2004 and 2016. Due to the coding of gestational age, to include neonates with a gestational age of 34 weeks 0 days requires that the criteria be neonates with a gestational age of less than 35 completed weeks. These infants were identified using the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9) codes. This iNO procedure codes used were 00.12 and 3EOF7SD.

The dates were divided into two epochs, Epoch 1 was from 2004 to 2010 and Epoch 2 was from 2011 to 2016. The division was based on the release date of the NIH consensus statement. outcomes of interest included: mortality, bronchopulmonary dysplasia (BPD), acute kidney injury, intraventricular hemorrhage), periventricular leukomalacia (PVL), length of stay (LOS), mechanical ventilation, disseminated intravascular coagulation, and cost of hospitalization. Demographic variables collected were gestational age, birth weight, sex, race, congenital diaphragmatic hernia, insurance type, hospital type, and hospital region. Congenital heart disease (CHD) was split into patent ductus arteriosus (PDA) and all other congenital heart defects. Small for gestational age (SGA) was presumed to be defined as weight less than the 10th percentile on the Fenton growth chart. BPD was classified as "yes" if a patient had an ICD code for BPD or chronic lung disease.

Frequency, median, and interquartile range were used for descriptive analysis. χ^2 or Fischer's exact tests were used for categorical variables, and Mann–Whitney U was used for statistical comparison. Mann–Kendall test was used for trend analysis. Analysis was performed by SPSS software, v25 (SPSS, Inc). The symbol, "a," is used in tables when the event frequency is 1–10 per data use agreement with HCUP.

3 | RESULTS

There were 2,412,574 neonates less than 35 weeks identified between 2004 and 2016. The characteristics of neonates less than 35 weeks are shown in Table 1. There was an increase in preterm neonates delivered in teaching hospitals, 64.9%–74.6% between Epoch 1 and 2, respectively. There were 4865 (0.2%) neonates who received iNO. There was a significant increase in iNO during 2011–2016 compared to 2004–2010 ($p < 0.001$). The highest use occurred during 2010 (Figure 1). The majority of iNO was used among neonates <27 weeks gestational age in both Epochs (Figure 2). The lowest usage occurred among neonates born at 31–32 weeks. There was a significant increase in iNO use from 19.8% to 22.7% between epochs among neonates born at ≤24 weeks (Figure 2). There was a significant decrease from 14.3% to 11.2% between epochs among neonates born 29–30 weeks. Figure 3 demonstrates iNO usage by gestational age among all neonates born during each Epoch. There was an increase in usage during Epoch 2. Usages were greatest among infants <27 weeks gestational age. No gestational age group had usage exceeding 1% of all neonates born in that gestational age.

Some outcomes were improved in Epoch 2 while other diagnoses increased (Table 2). There was a significantly lower percentage of deaths in Epoch 2, 32.9%, compared with Epoch 1, 37.1% (odds ratio = 1.2, 95% confidence interval: 1.07–-1.35). There was a significant increase in SGA infants who used iNO ($p < 0.001$) during Epoch 2. There were significantly fewer neonates who required mechanical ventilation during Epoch 2 ($p < 0.001$), but significantly more infants were diagnosed with BPD and PVL. The LOS was significantly longer in Epoch 2 with a median of 55 days and an interquartile range, 15–102 ($p < 0.001$). The cost was significantly higher during Epoch 2 ($p < 0.001$). BPD, PVL, and LOS were also evaluated during the same period for all infants <35 weeks gestational regardless of iNO use. LOS was significantly longer during Epoch 2 with

TABLE 1 Characteristics of neonates <35 weeks

	2004–2010 (*N* = 1,363,165)		2011–2016 (*N* = 1,049,409)		
	Frequency	%	Frequency	%	*p*
Gestational age, wk					<0.001
≤24	92,364	6.8	70,911	6.8	
25–26	82,889	6.1	68,130	6.5	
27–28	109,483	8.0	86,072	8.2	
29–30	156,782	11.5	117,066	11.2	
31–32	287,500	21.1	212,968	20.3	
33–34	634,148	46.5	494,261	47.1	
Birth weight, g					<0.001
<1000	37,142	2.8	26,736	2.7	
1000–1499	17,4274	13.3	138,248	14.2	
1500–1999	24,4202	18.7	183,242	18.8	
2000–2500	382,133	29.2	280,873	28.9	
>2500	350,916	26.8	264,923	27.2	
Sex (male)	723,955	53.1	563,954	53.8	<0.001
Race					<0.001
White	507,665	49.0	440,989	47.7	
Black	213,517	20.6	204,784	22.2	
Hispanic	206,604	19.9	168,870	18.3	
Asian	38,814	3.7	38,911	4.2	
Native American	9491	0.9	7435	0.8	
Other	59,745	5.8	63,024	6.8	
Primary payer					<0.001
Public insurance	653,176	48.0	548,407	52.4	
Private insurance	607,113	44.6	427,269	40.8	
Self-pay	52,317	3.8	30,736	2.9	
Other	46,540	3.4	40,737	3.9	
Hospital type					<0.001
Teaching	626,791	64.9	779,877	74.6	
Nonteaching	339,007	35.1	265,791	25.4	
Hospital bed size					<0.001
Small	69,037	7.1	108,988	10.4	
Medium	228,504	23.7	273,954	26.2	
Large	668,258	69.2	662,726	63.4	
Region					<0.001
Northeast	161,623	16.6	160,253	15.3	
Midwest	204,418	21.0	235,358	22.4	
South	395,657	40.6	429,698	40.9	
West	213,309	21.9	224,100	21.4	
Disposition of patient					<0.001
Routine discharge	1,054,498	77.4	845,678	80.7	
Transfer	222,240	16.3	143,720	13.7	
Died	85,422	6.3	58,482	5.6	

Note: χ^2 or Fisher's exact tests were used for analysis.

a median of 18 versus 15 days ($p < 0.001$). LOS was significantly longer for infants who required iNO ($p < 0.001$). BPD was significantly higher during Epoch 2, 6.6% versus 6.0% ($p < 0.001$). PVL was significantly higher during Epoch 2, 0.8% versus 0.5% ($p < 0.001$).

During Epoch 2, there were significantly more neonates treated with iNO who had CHD (excluding isolated PDA) ($p < 0.001$), but there was no difference in iNO use for preterm neonates with a congenital diaphragmatic hernia (Table 2).

Mortality and LOS were further analyzed for subpopulations of interest (Table 3). Mortality was not statistically different between Epochs 1 and 2 for neonates identified as being SGA and that develop BPD, mortality was significantly lower in Epoch 2 for neonates with CHD. LOS was significantly longer in Epoch 2 for all three subgroups.

4 | DISCUSSION

iNO continues to be a rescue therapy for preterm neonates <35 weeks with severe and refractory hypoxic respiratory failure. The trend over time is increased usage despite the NIH consensus statement. This study continues to support the findings of earlier studies regarding the continued increased use among preterm infants.[32] The use of iNO in premature infants with confirmed persistent pulmonary hypertension of the newborn is supported by the American Thoracic Society/American Heart Association[33] and the Pediatric Pulmonary Hypertension Network,[34] as well as the European Pediatric Pulmonary Vascular Disease Network.[35] The continued increase in the use of iNO despite the consensus statement may be related to the difficulty in predicting which infants will respond to iNO as well as difficulties in obtaining echocardiograms before initiating iNO. Possibly as more providers have success with using iNO, the impression is that there is little risk or downsides to a trial of iNO. However, implementing evidence-based guidelines for initiation and weaning of iNO will help us to reduce prolonged use and overuse in resistant populations.[36]

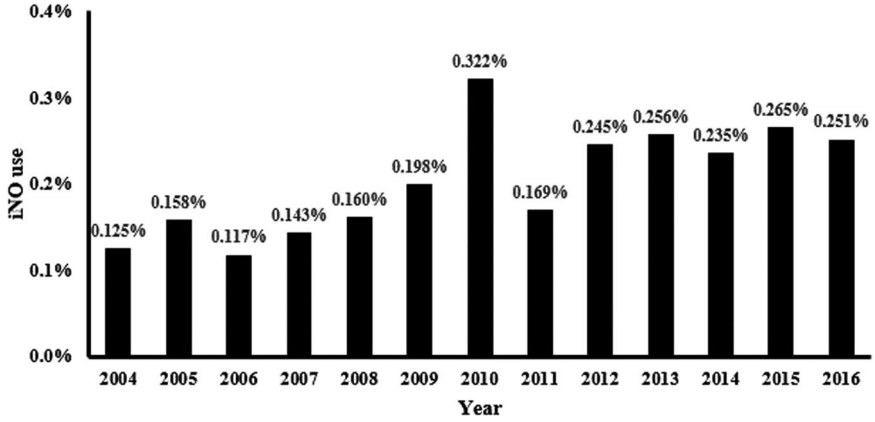

FIGURE 1 Trend of iNO use in preterm infants (GA < 35 weeks) by year from 2004 to 2016. Significant increase in iNO during 2011–2016 compared to 2004–2010 ($p < 0.001$). GA, gestational age; iNO, inhaled nitric oxide

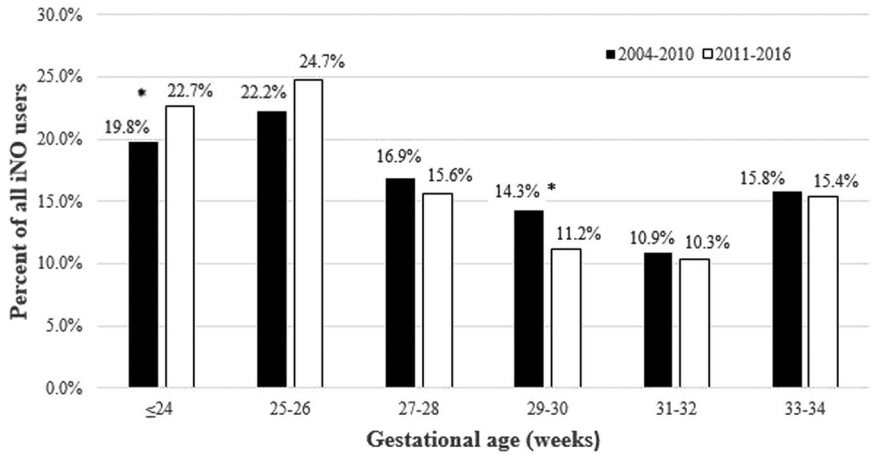

FIGURE 2 Distribution of iNO use by gestational age, $^*p < 0.05$ between groups. iNO, inhaled nitric oxide

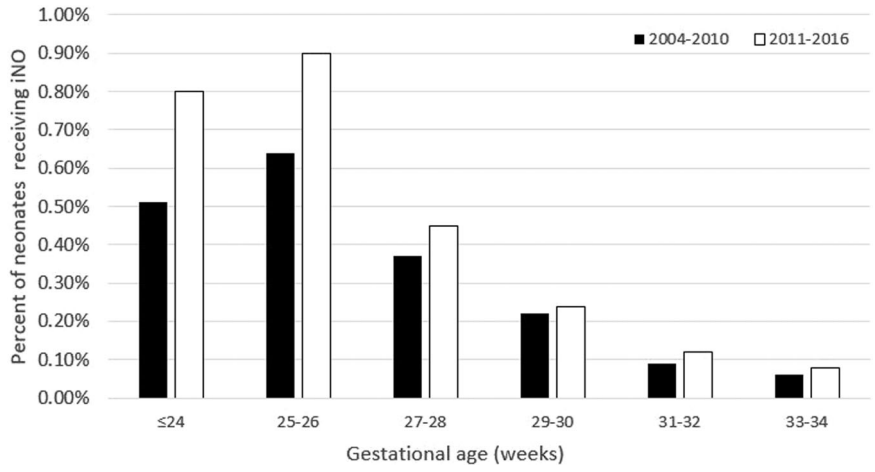

FIGURE 3 Percentage of neonates in each gestational age group who received iNO during each Epoch. The denominator is from the full group from Table 1. iNO, inhaled nitric oxide

This study is one of the few[25,37] to demonstrate a decrease in mortality during a period of time with increased iNO usage. This cannot be considered causal as there is not enough granularity in the data and there is no way to account for potential medical practice changes. This study did not show improvement in mortality among neonates who were SGA; in fact, mortality was higher in neonates who were SGA and received iNO than the pooled preterm infants with iNO needs. This may reflect lethality of the potential underlying cause of poor growth such as chromosomal anomalies or other congenital anomalies. Despite the overall higher mortality rates, the LOS was longer for infants who were SGA suggesting they may have late-onset pulmonary hypertension. This study, like others,[8,15,17–19,22–25] showed no significant improvement in mortality among infants who were diagnosed with BPD, but there was an associated increase in LOS.

This is believed to be the first report of improved mortality among preterm infants with CHD (exclusive of isolated PDA) with hypoxic respiratory failure requiring iNO. It is not uncommon for

TABLE 2 Outcomes among neonates who received iNO

	2004–2010 (*N* = 2378)	2011–2016 (*N* = 2487)	OR (95% CI)	*p*
Mortality, *n* (%)	881 (37.1)	819 (32.9)	1.20 (1.07–1.35)	0.003
Congenital heart disease except for PDA, *n* (%)	264 (11.1)	462 (18.6)	0.55 (0.47–0.64)	<0.001
PDA, *n* (%)	1 193 (50.2)	1 261 (50.7)	0.98 (0.87–1.09)	0.698
Congenital diaphragmatic hernia, *n* (%)	45 (1.9)	60 (2.4)	0.78 (0.53–1.15)	0.237
Hypotension, shock, vasopressor use, *n* (%)	728 (30.6)	1 006 (40.5)	0.65 (0.58–0.73)	<0.001
Acute kidney injury, *n* (%)	217 (9.1)	234 (9.4)	0.97 (0.80–1.17)	0.733
Intraventricular hemorrhage, *n* (%)	711 (29.9)	755 (30.4)	0.98 (0.87–1.11)	0.735
Intestinal perforation, *n* (%)	(0.2)[a]	15 (0.6)	0.28 (0.09–0.84)	0.020
DIC, *n* (%)	125 (5.3)	118 (4.7)	1.11 (0.86–1.44)	0.430
Small for GA[b], *n* (%)	55 (2.3)	179 (7.2)	0.31 (0.22–0.42)	<0.001
Bronchopulmonary dysplasia, *n* (%)	836 (35.2)	1 163 (46.8)	0.62 (0.55–0.69)	<0.001
Periventricular leukomalacia, *n* (%)	54 (2.3)	134 (5.4)	0.41 (0.30–0.56)	<0.001
Mechanical ventilation, *n* (%)	2323 (97.7)	2032 (81.7)	9.46 (7.11–12.59)	<0.001
Length of stay, days (IQR)[c]	46 (10-88)	55 (15–102)		<0.001
Cost of hospitalization ($)[c], median (IQR)	324,562 (109,614–613,088)	640,902 (196,215–1,255,714)		<0.001

Note: Data are expressed in frequency (%); χ^2 or Fisher's exact tests were used for analysis except with data.

Abbreviations: CI, confidence interval; DIC, disseminated intravascular coagulopathy; GA, gestational age; iNO, inhaled nitric oxide; IQR, interquartile range; OR, odds ratio; PDA, patent ductus arteriosus.

[a]Event frequency 1–10 per data use agreement.

[b]Less than 10% percentile.

[c]Expressed in median (interquartile range); Mann–Whitney U test was used for analysis.

TABLE 3 Subgroup analysis

	2004–2010	2011–2016	OR (95% CI)	*p*
SGA (*N* = 478)	*N* = 180	*N* = 298		
Mortality, *n* (%)	80 (44.4)	132 (44.3)	1.01 (0.69–1.46)	0.975
LOS (days), median (IQR)	57 (10–97)	80 (12–139)		0.001
CHD (*N* = 3180)	*N* = 1455	*N* = 1724		
Mortality, *n* (%)	457 (31.4)	478 (27.7)	1.19 (1.02–1.39)	0.025
LOS (days), median (IQR)	54 (14–99)	70 (24–111)		<0.001
BPD (*N* = 2000)	*N* = 835	*N* = 1165		
Mortality, *n* (%)	147 (17.6)	182 (15.6)	1.15 (0.91–1.46)	0.255
LOS (days), median (IQR)	88 (60–123)	97 (63–135)		0.021

Note: Data are expressed in frequency (%); χ^2 or Fisher's exact tests were used for analysis except with data expressed in median (interquartile range); Mann–Whitney U test was used for analysis. BPD was determined by using ICD codes for bronchopulmonary dysplasia and chronic lung disease.

Abbreviations: BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CI, confidence interval; ICD, International Classification of Diseases; IQR, interquartile range; LOS, length of stay; OR, odds ratio; SGA, small for gestational age.

certain CHD to have iNO responsive pulmonary hypertension which could be theoretically compounded by respiratory distress syndrome.

The increase in the number of preterm infants delivered in teaching hospitals increased from 65% to 75% (Table 1). During the study time, the American Board of Pediatrics Workforce Project Team has published data showing an increase in first-year pediatric trainees by nearly 500 trainees.[38] Additional searching has shown at least 10 new general pediatric residency programs via multiple searches through the National Resident Matching Program (citation not available). Another possibility is as academic medical centers

acquire smaller community hospitals, the community hospital can have an academic or teaching affiliation.

The LOS was significantly longer and the cost of hospitalization was significantly higher. The increase in LOS in Epoch 2 was also seen among infants SGA, diagnosed with BPD, or CHD (Table 3). The neonates in both epochs were similar, despite statistical significance likely reflective of the large sample size. Although, the significant increase in infants classified as SGA or with CHD (Table 2) is unlikely to be due to the large sample size. This change may be related to an increase in the resuscitation of these infants or an increase in assistive reproductive technologies as there is an increased risk for CHDs and fetal growth restriction. However, the increase in infants being treated at small hospitals may be a result of the expansion of the number of Levels II and III neonatal intensive care units (NICUs).

The fact that the majority of iNO use is in neonates with birth gestational age <27 weeks is interesting and mimics several other studies.[39–41] Speculation is that these infants have higher rates of hypoxic respiratory failure (with or without documented pulmonary hypertension) due to respiratory distress syndrome and higher pulmonary vascular resistance and less responsiveness to oxygen.[42,43] If these infants are not responsive to ventilator management, for rescue, they may be started on iNO.[7,44] This trend is likely to continue due to increasing rates of resuscitation among extremely premature neonates born at periviable gestations.

This is a large cross-sectional national study. The ability to have a large sample size from the dataset allows for comparisons between time periods and evaluation of national trends. The size allows for the identification of significant changes in smaller quantities. The likelihood of under classification is low in the administrative dataset as the cost of iNO is high and billing for its use is unlikely to be missed. Another advantage is the ability to evaluate additional variables of interest which are normally rare in occurrence.

The major limitations to this study are due to a lack of granularity. Due to the data source, we are unable to link the timing of interventions with certain outcomes (i.e., when iNO was given, for how many days, and whether the infant was intubated during that time). In addition, we cannot determine how the diagnosis of pulmonary hypertension was decided, and we cannot know exactly which definition was used by a provider to designate BPD (BPD for this study was determined if an appropriate ICD code was given to the infant). Missing data can be a limitation for some studies. This study does have missing data which decreased the sample size; however, the sample size is large in comparison to single-center studies such that missing data is unlikely to skew the data and/or results. However, despite these limitations, NIS has been shown to be comparable to disease-specific databases[45] and multistate inpatient electronic medical record databases.[46] The inclusion of preterm neonates born at 34 1/7–34 6/7 weeks may be controversial particularly related to the potential for bias; however, their inclusion was determined before evaluation of the data. For FDA approval, two major studies were used,[47] Neonatal Inhaled Nitric Oxide Study (NINOS) and Clinical Inhaled Nitric Oxide Research Group Investigation (CINRGI). The NINOS[1] study did not include any neonate born at 34 0/7 weeks and older. On the other hand, the CINRGI[48] study reports inclusion criteria as >34 weeks; however, they do not include gestational age in their patient characteristic table. In this case, if using birth weight as a surrogate, the CINRGI likely had few neonates 34 1/7–34 6/7 weeks. When completing the data analysis for this study, we felt that neonates born at <35 weeks should be included because most NICUS automatically admit neonates born <35 weeks due to prematurity. Additionally, on review of our data and results neonates born at a gestational age of 33–34 weeks only compromised 15% of iNO recipients (Figure 2), thus they will not cause significant bias.

In conclusion, iNO use in preterm neonates continues to rise across the nation. This may be due to the increase in research suggesting that certain populations or pathologies may have a different response. Askie et al. showed a benefit for sub-population use with African–American neonates at high risk for developing BPD.[49] There is increasing evidence that certain populations have better responses to iNO.[50–56]

Despite the increase in iNO use, pooled mortality remained greater than 30%. Thus, the information gathered via this epidemiologic evaluation suggests further research to describe mortality amongst iNO recipients by gestational age, the timing of initiation, and by underlying etiology of pulmonary hypertension is warranted; this also applies to the changes seen related to improvement in mortality among preterm infant with CHD who receive iNO. Ultimately, we believe the addition of this epidemiologic data will help aid in further hypothesis development to further research for our smallest and sickest patients.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Allison Peluso: Conceptualization (lead); formal analysis (supporting); investigation (lead); methodology (lead); writing – original draft (lead); and writing – review and editing (lead). **Hasan F Othman:** Data curation (lead); formal analysis (lead); investigation (equal); software (lead); and writing – review and editing (equal). **Sreenivas Karnati:** Formal analysis (supporting); methodology (supporting); and writing – review and editing (equal). **Ibrahim Sammour:** Formal analysis (equal); validation (equal); and writing – review and editing (equal). **Hany Aly:** Conceptualization (supporting); formal analysis (supporting); project administration (supporting); software (lead); supervision (lead); and writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Data can be accessed at https://www.hcup-us.ahrq.gov/tech_assist/centdist.jsp.

ORCID

Allison M. Peluso http://orcid.org/0000-0001-9825-0822
Hany Z. Aly http://orcid.org/0000-0001-7395-6394

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