Inhaled Nitric Oxide in Extremely Premature Neonates With Respiratory Distress Syndrome

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abstract

BACKGROUND: Inhaled nitric oxide (iNO) is increasingly prescribed to extremely premature neonates with respiratory distress syndrome (RDS). Most of this off-label use occurs during the first week of life. We studied this practice, hypothesizing that it would not be associated with improved survival.

METHODS: We queried the Pediatrix Medical Group Clinical Data Warehouse to identify all neonates born at 22 to 29 weeks' gestation from 2004 to 2014. In our study sample, we included singletons who required mechanical ventilation for treatment of RDS and excluded those with anomalies. The primary outcome was death before discharge. Through a sequential risk set approach, each patient who received iNO during the first 7 days of life ("case patient") was matched by using propensity scores to a patient who had not received iNO at a chronological age before the case patient's iNO initiation age (defined as the index age for the matched pair). The association between iNO status and in-hospital mortality was evaluated in a Cox proportional hazards regression model by using age as the time scale with patients entering the risk set at their respective index age.

RESULTS: Among 37 909 neonates in our study sample, we identified 993 (2.6%) who received iNO. The 2 matched cohorts each contained 971 patients. We did not observe a significant association between iNO exposure and mortality (hazard ratio, 1.08; 95% confidence interval, 0.94–1.25; $P = .29$).

CONCLUSIONS: Off-label prescription of iNO is not associated with reduced in-hospital mortality among extremely premature neonates with RDS.

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WHAT'S KNOWN ON THIS SUBJECT: Despite guidance from the National Institutes of Health and the American Academy of Pediatrics, inhaled nitric oxide is still commonly prescribed to extremely premature neonates. The majority of this off-label use occurs in the first week of life.

WHAT THIS STUDY ADDS: Among a large cohort of extremely premature neonates with respiratory distress syndrome, treatment with inhaled nitric oxide during the first week of life was not associated with improved in-hospital survival.

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Inhaled nitric oxide (iNO) is an approved therapy for term and near-term neonates with hypoxic respiratory failure. Although its safety and efficacy are well established in these populations,[1–3] iNO neither improves survival nor prevents long-term morbidity in neonates <34 weeks' gestation. Taking into account the results of randomized controlled trials (RCTs),[4–14] systematic reviews,[15,16] and 1 meta-analysis of individual patient data,[17] both the National Institutes of Health and the American Academy of Pediatrics have issued statements discouraging the use of iNO in premature neonates.[18,19]

Despite the published evidence and expert guidance to the contrary, there has been a trend toward the use of iNO in premature neonates. Such off-label prescription has increased in recent years,[20–22] almost entirely because of rising rates of use in neonates <30 weeks' gestation.[21,22] Although these extremely premature neonates represent <1% of births in the United States,[23] they now account for nearly half of all the iNO used in US NICUs each year.[21] Expert opinion appears to be changing as well. The American Heart Association and American Thoracic Society recently recommended that "iNO can be beneficial for preterm infants with. . .[persistent pulmonary hypertension of the newborn]."[24] Similar recommendations were issued by the Pediatric Pulmonary Hypertension Network, with iNO being considered "preferred over other pulmonary vasodilators" in premature neonates with severe pulmonary hypertension.[25]

It is important to note that the more recent guidelines pertain to a specific subpopulation of premature neonates, namely those whose hypoxic respiratory failure is accompanied by persistent pulmonary hypertension of the newborn (PPHN). Although respiratory distress syndrome (RDS) occurs commonly among neonates <34 weeks' gestation, only a small percentage also suffer from PPHN physiology.[26] Given the infrequency of concomitant PPHN in the setting of RDS, it is unlikely that a randomized trial of iNO will be conducted in the near future.[25,27] Thus, alternative study designs have been proposed as a more feasible means by which to acquire evidence on which to base our practices.[25,27,28] With this in mind, we conducted the current study to determine if iNO improves in-hospital survival among extremely premature neonates with RDS. We hypothesized that iNO would not improve survival for all patients, although we expected to find improved survival among those with concomitant PPHN.

METHODS

Study Design

We performed a retrospective cohort study by using data from the Clinical Data Warehouse (CDW), which comprises >1 million neonates who received care in a Pediatrix Medical Group (PMG) NICU.[21] The study was approved by the Greenville Memorial Hospital Institutional Review Board (Greenville, SC) and was deemed exempt by the Mayo Clinic Institutional Review Board (Rochester, MN).

Study Setting and Population

We included neonates who required admission to a PMG NICU and were discharged between January 1, 2004, and December 31, 2014. We queried specific CDW tables, namely "patients," "admissions," "diagnoses," "medications," and "respiratory support." We included in our study singletons born at 22 to 29 weeks' gestation who required mechanical ventilation for treatment of RDS. We excluded from our analysis neonates who died in the delivery room, those who were admitted for comfort care only, and those with pulmonary hypoplasia or major congenital anomalies.

Patient Characteristics and Outcomes

For each patient, we obtained baseline maternal and neonatal characteristics (Table 1). The primary outcome was mortality, which we defined as death before discharge. Secondary outcomes were any stage of necrotizing enterocolitis (NEC); retinopathy of prematurity requiring treatment (tROP); chronic lung disease (CLD), which we defined as a requirement for supplemental oxygen or any form of pressure support at 36 weeks' corrected gestational age (CGA); and periventricular leukomalacia (PVL).

Data Analysis

Because iNO exposure was not randomly assigned in this retrospective cohort, we used propensity score (PS) matching to reduce the imbalance of measured baseline characteristics between patients who received iNO during the first 7 days of life and their matched referents.[29] Because iNO could have been initiated at any time during the first 7 days of life, we used a risk set approach to match a patient who initiated iNO on day t ("case patient") with another patient ("referent") with similar baseline characteristics who had not received iNO as of day t.

First, we created a risk set of all patients "at risk" for receiving iNO on day $t = 0$. Using all the patients in this risk set, we fit a multivariate logistic model to estimate PS values (defined as the probability that a patient would receive iNO on day $t = 0$ and conditional on the measured baseline covariates). For each patient who received iNO on day $t = 0$, 1 patient was randomly selected without replacement from the pool of patients meeting the matching criteria who did not receive iNO on day $t = 0$. Patients were matched on the logit of the PS by using calipers of width 0.2

TABLE 1 Baseline Characteristics of Full Cohort and Matched Cohort by iNO Status

Characteristic	Full Cohort			Matched Cohort		
	iNO Within First 7 d (*N* = 993)	No iNO Within First 7 d (*N* = 36 916)	Total (*N* = 37 909)	iNO (*N* = 971)	Referent (*N* = 971)	Total (*N* = 1942)
Maternal characteristics, *n* (%)						
Prolonged ROM	237 (23.9)	5471 (14.8)	5708 (15.1)	229 (23.6)	191 (19.7)	420 (21.6)
Oligohydramnios	9 (0.9)	254 (0.7)	263 (0.7)	8 (0.8)	9 (0.9)	17 (0.9)
Antenatal steroids given	641 (64.6)	25 978 (70.4)	26 619 (70.2)	629 (64.8)	618 (63.6)	1247 (64.2)
Infant characteristics						
Respiratory diagnosis group, *n* (%)						
RDS	332 (33.4)	36 046 (97.6)	36 378 (96.0)	332 (34.2)	332 (34.2)	664 (34.2)
RDS and pulmonary hypertension	661 (66.6)	870 (2.4)	1531 (4.0)	639 (65.8)	639 (65.8)	1278 (65.8)
Gestational age, wk, mean (SD)	25.7 (1.9)	26.4 (1.9)	26.3 (1.9)	25.7 (1.9)	25.6 (1.9)	25.7 (1.9)
Birth wt, kg, mean (SD)	0.84 (0.28)	0.91 (0.27)	0.91 (0.27)	0.84 (0.28)	0.82 (0.28)	0.83 (0.28)
Birth size assessment, *n* (%)						
SGA	155 (15.6)	4760 (12.9)	4915 (13.0)	151 (15.6)	162 (16.7)	313 (16.1)
AGA	728 (73.3)	29 069 (78.7)	29 797 (78.6)	713 (73.4)	716 (73.7)	1429 (73.6)
LGA	110 (11.1)	3087 (8.4)	3197 (8.4)	107 (11.0)	93 (9.6)	200 (10.3)
Sex, *n* (%)						
Female	399 (40.2)	16 908 (45.8)	17 307 (45.7)	393 (40.5)	414 (42.6)	807 (41.6)
Male	593 (59.7)	19 998 (54.2)	20 591 (54.3)	578 (59.5)	557 (57.4)	1135 (58.4)
Unknown	1 (0.1)	10 (0.0)	11 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race, *n* (%)						
White	407 (41.0)	14 254 (38.6)	14 661 (38.7)	398 (41.0)	391 (40.3)	789 (40.6)
Asian American	19 (1.9)	909 (2.5)	928 (2.4)	19 (2.0)	20 (2.1)	39 (2.0)
African American	300 (30.2)	11 428 (31.0)	11 728 (30.9)	289 (29.8)	299 (30.8)	588 (30.3)
Hispanic	201 (20.2)	8133 (22.0)	8334 (22.0)	200 (20.6)	191 (19.7)	391 (20.1)
Other	66 (6.6)	2192 (5.9)	2258 (6.0)	65 (6.7)	70 (7.2)	135 (7.0)
Discharge year, *n* (%)						
2004	34 (3.4)	2893 (7.8)	2927 (7.7)	34 (3.5)	33 (3.4)	67 (3.5)
2005	41 (4.1)	3152 (8.5)	3193 (8.4)	41 (4.2)	42 (4.3)	83 (4.3)
2006	51 (5.1)	3436 (9.3)	3487 (9.2)	51 (5.3)	52 (5.4)	103 (5.3)
2007	81 (8.2)	3681 (10.0)	3762 (9.9)	80 (8.2)	83 (8.5)	163 (8.4)
2008	89 (9.0)	3666 (9.9)	3755 (9.9)	89 (9.2)	87 (9.0)	176 (9.1)
2009	104 (10.5)	3509 (9.5)	3613 (9.5)	103 (10.6)	99 (10.2)	202 (10.4)
2010	105 (10.6)	3520 (9.5)	3625 (9.6)	104 (10.7)	109 (11.2)	213 (11.0)
2011	101 (10.2)	3331 (9.0)	3432 (9.1)	99 (10.2)	98 (10.1)	197 (10.1)
2012	135 (13.6)	3388 (9.2)	3523 (9.3)	133 (13.7)	129 (13.3)	262 (13.5)
2013	128 (12.9)	3118 (8.4)	3246 (8.6)	123 (12.7)	132 (13.6)	255 (13.1)
2014	124 (12.5)	3222 (8.7)	3346 (8.8)	114 (11.7)	107 (11.0)	221 (11.4)
Inborn or outborn status, *n* (%)						
Inborn	750 (75.5)	30 708 (83.2)	31 458 (83.0)	734 (75.6)	732 (75.4)	1466 (75.5)
Outborn	243 (24.5)	6208 (16.8)	6451 (17.0)	237 (24.4)	239 (24.6)	476 (24.5)
Surfactant given, *n* (%)	886 (89.2)	31 432 (85.1)	32 318 (85.3)	865 (89.1)	857 (88.3)	1722 (88.7)
Maximum support rating on days 0–2, *n* (%)						
Conventional ventilator	196 (19.7)	27 076 (73.3)	27 272 (71.9)	196 (20.2)	219 (22.6)	415 (21.4)
High-frequency oscillator	797 (80.3)	9840 (26.7)	10 637 (28.1)	775 (79.8)	752 (77.4)	1527 (78.6)
At least 1 vasopressor reported on days 0–3, *n* (%)	726 (73.1)	10 099 (27.4)	10 825 (28.6)	706 (72.7)	695 (71.6)	1401 (72.1)

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

of the SD of the logit of the PS and the presence or absence of pulmonary hypertension. We then repeated this sequential process for each of the days $t = 1$ to $t = 7$, only excluding patients from each risk set who had died, been transferred, or received iNO before time *t*. Last, we combined all matched pairs (case patients and their matched referents) into a single cohort for analysis. The date of iNO initiation for the iNO case patient was defined as the "index date" for both the iNO case patient and their matched referent.

We assessed covariate imbalance between the treated (iNO) and referent groups by evaluating the standardized difference for each baseline covariate. The standardized difference for a continuous covariate was defined as the absolute difference in group means divided by an estimate of the pooled SD. The derivation is similar for nominal covariates. A standardized difference <0.10 denotes negligible covariate imbalance between groups.[30]

We used a Cox proportional hazards model to assess the association between iNO status and in-hospital mortality by using age as the time scale with patients entering the risk set at their respective age at the index date.[31] By using the counting process formulation of a Cox model, patients entered the analysis at their index age (left truncation) and exited at their death or discharge age. Robust sandwich covariance estimates were used in the Cox models to account for patients included in both cohorts (referent patients who subsequently received iNO). Associations were summarized by using the hazard ratio (HR) and corresponding 95% confidence interval (CI).

We employed the same time-to-event analysis methods to assess NEC as a secondary outcome. For the remaining 3 secondary outcomes, we identified separate PS-matched subcohorts of patients who were eligible for evaluation of these diagnoses. For tROP, we restricted the starting cohort to patients with retinopathy of prematurity (ROP) evaluated; for CLD, we restricted the starting cohort to patients still hospitalized at 36 weeks' CGA; and for PVL, we restricted the starting cohort to patients with brain imaging. Because iNO exposure status was known by the time each of these outcomes was clinically evaluated, we estimated PS values and performed matching in just 1 step for each subcohort. We then considered iNO exposure status as a baseline covariate and evaluated the association between iNO and each secondary outcome using logistic regression. Associations were summarized by using the odds ratio (OR) and corresponding 95% CI.

We used similar analysis methods to assess the RDS and PPHN and the RDS subgroups separately. We adjusted for unbalanced covariates in the PS-matched cohorts within each subgroup in the regression models evaluating the outcomes. All calculated *P* values were 2-sided, and *P* values <.05 were considered statistically significant. We performed statistical analyses by using SAS version 9.4 software (SAS Institute, Inc, Cary, NC).

RESULTS

There were 92 635 neonates born at 22 to 29 weeks' gestation and admitted to PMG NICUs from 2000 to 2014. As shown in Fig 1, patients were sequentially excluded because of the presence of pulmonary hypoplasia and/or major congenital anomalies, nonsingleton birth status, or no requirement for mechanical ventilation during the first 2 days of life. Of the remaining neonates, those discharged from 2000 to 2003 were excluded from the analysis because of an iNO rate of use of <1% in each of those years.

In the unmatched cohort of 37 909 neonates with RDS, 993 (2.6%) received iNO during the first week of life. The majority of iNO exposure occurred early in life: 439 (44.2%) initiated on day of birth, 271 (27.3%) initiated on day 1, 106 (10.7%) initiated on day 2, 50 (5.0%) initiated on day 3, and 127 (12.8%) initiated from days 4 to 7. We observed a significant imbalance in several baseline characteristics between the iNO-exposed and unexposed groups (Table 1). Neonates treated with iNO were more often born after prolonged rupture of membranes (ROM) and less frequently had received antenatal steroid treatment. Moreover, neonates in the iNO group were far more likely to be diagnosed with concomitant PPHN (66.6% vs 2.4%), require high frequency oscillatory ventilation (80.3% vs 26.7%), or receive vasopressor therapy during the first 3 days of life (73.1% vs 27.4%).

To adjust for the imbalance in observed baseline covariates, we created a cohort matched on PS values and PPHN status. The matched iNO and referent groups each contained 971 patients and were balanced for all observed covariates with all standardized differences below the recommended threshold of 0.10 (Fig 2, Table 1). The matched cohort was characterized by high rates of pulmonary hypertension (65.8%), requirement for high frequency oscillatory ventilation (78.6%), and vasopressor therapy during the first 3 days of life (72.1%).

Complete Matched Cohort

Among the 971 patients in the iNO group, 348 died in-hospital at a median age of 6 days (interquartile range [IQR]: 2–14 days) and the remaining 623 were discharged after a median length-of-stay of 89 days (IQR: 65–114 days). Among the matched referents, 325 died at a median age of 6 days (IQR: 2–15 days), and the remaining 646 referents were discharged after a median length-of-stay of 88 days (IQR: 58–112 days). One hundred seventy-one of the matched referents went on to receive iNO therapy at a median age of 2 days (IQR: 1–3 days). We did not observe a significant association between iNO exposure and mortality (HR, 1.08; 95% CI, 0.94–1.25; *P* = .29; Fig 3).

NEC was diagnosed in 112 iNO-exposed patients at a median age of 23 days (IQR: 11–35 days) and in 107 matched referents at a median age of 27 days (IQR: 14–40 days). Our analysis did not reveal a significant association between iNO exposure and NEC (HR, 1.07; 95% CI, 0.84–1.37; *P* = .59; Supplemental Fig 5). Similarly, iNO exposure during the first 7 days of life was

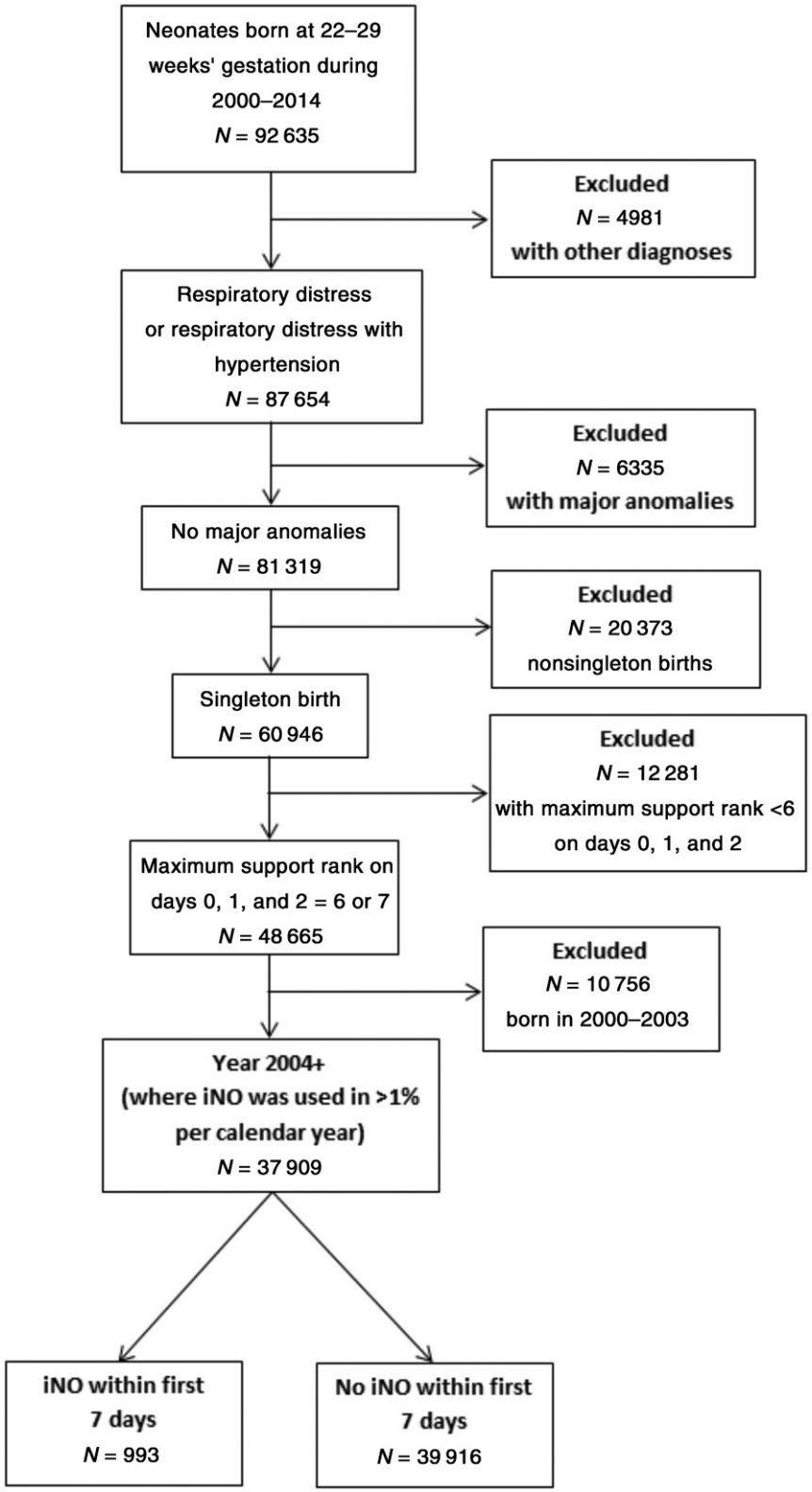

FIGURE 1
Consolidated Standards of Reporting Trials flow diagram.

not associated with higher or lower rates of tROP, CLD, or PVL (Supplemental Table 2).

Cohorts Stratified by PPHN Status

To determine if the outcomes of early iNO treatment might vary depending on PPHN status, we separated RDS patients in the matched cohort into those with and those without a concomitant diagnosis of PPHN. Because patients in these 2 subcohorts were matched for PS and respiratory diagnosis, the iNO and referent groups in each remained fairly balanced for all observed covariates (Supplemental Fig 6, Supplemental Table 3). Covariates with residual imbalance in the PS-matched cohorts were adjusted for in the regression models evaluating the outcomes.

Contrary to our second hypothesis, we did not observe a significant association between iNO exposure and mortality among RDS patients with concomitant PPHN (HR, 0.96; 95% CI, 0.81–1.13; $P = .60$, adjusted for birth weight and prolonged ROM; Fig 4). However, somewhat surprisingly, iNO exposure was associated with higher mortality among neonates whose RDS was not accompanied by PPHN (HR, 1.67; 95% CI, 1.27–2.20; $P < .001$, adjusted for birth size and maximum support rating; Fig 4).

In neither subcohort did we find an association between iNO exposure and NEC (RDS and PPHN: HR, 1.13; 95% CI, 0.85–1.50; $P = .42$, adjusted for birth weight and prolonged ROM. RDS: HR, 1.05; 95% CI, 0.66–1.66; $P = .85$, adjusted for birth size and maximum support rating; Supplemental Fig 7). As shown in Supplemental Table 4, iNO exposure during the first 7 days of life was not associated with higher or lower rates of tROP, CLD, or PVL in both subgroups.

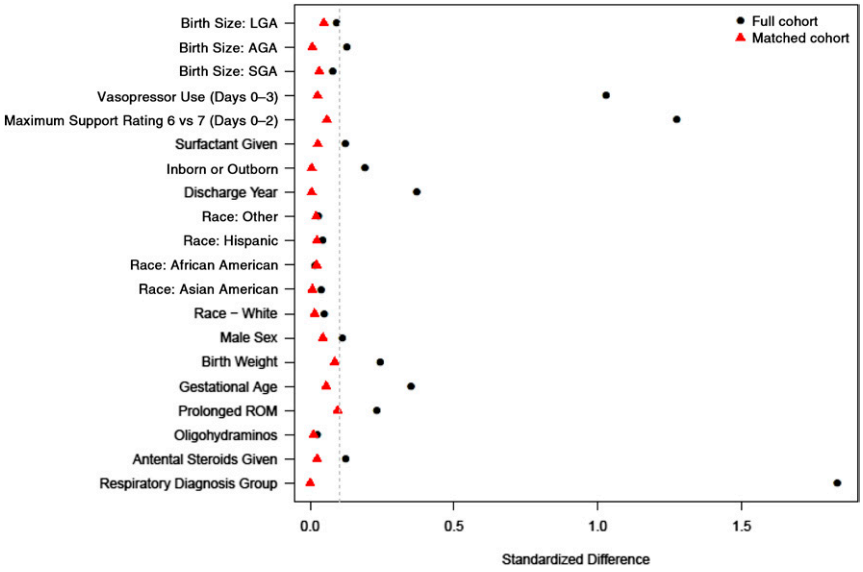

FIGURE 2

Standardized differences (absolute value) for each covariate used in the derivation of the PSs. In the PS-matched cohort, the covariates were more balanced between the 2 groups, with all standardized differences below the 0.10 threshold. AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

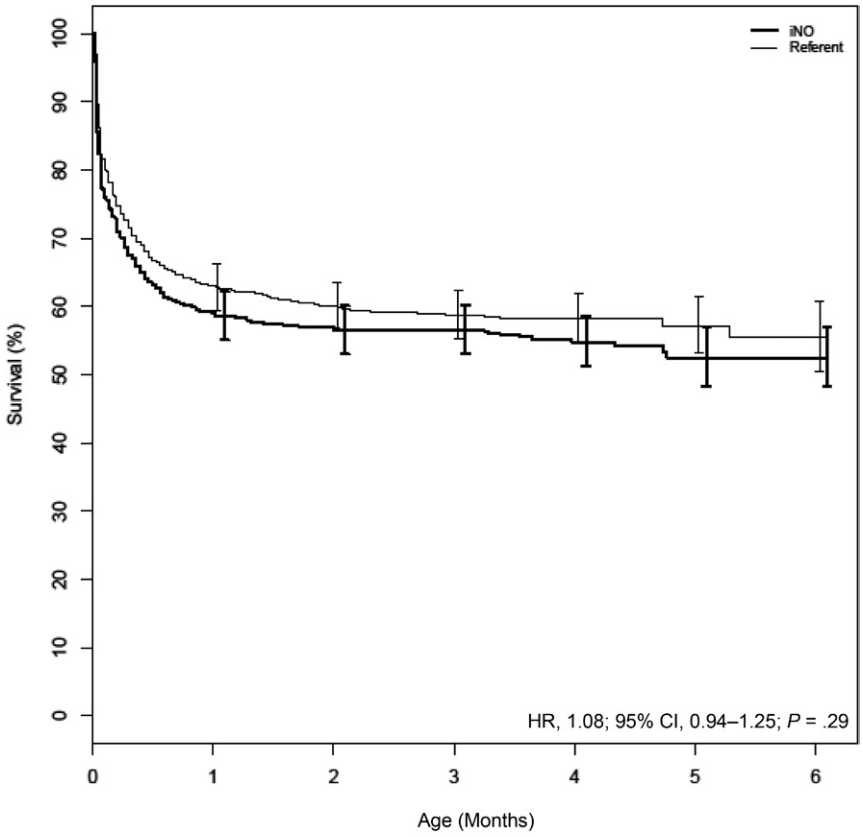

FIGURE 3

Overall survival by iNO status of patients in the matched cohort. The survival estimates were derived from a Cox model, with patients entering the risk set at their respective age at the index date.

DISCUSSION

We demonstrate that off-label prescription of iNO is not associated with improved survival in a large cohort of extremely premature neonates with RDS. Among subjects whose RDS was associated with PPHN, treatment with iNO did not affect survival beyond the first week of life. In the absence of PPHN, iNO was prescribed rarely (<1%), although its use was associated with increased mortality. The demographic characteristics and outcomes of our matched cohort were similar to those of the 2 largest US clinical trials of early iNO.[9,12] Likewise, among nearly 38 000 subjects in the overall cohort, the prevalence of PPHN was similar to that which has been reported previously.[26,32,33]

Despite the risks identified by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development,[9,34] extremely premature neonates receive nearly half of the iNO administered in US NICUs.[21] Much of this iNO may be prescribed to the most critically ill of these infants because rates of use are highest among regional centers.[22] This leads us to speculate that US neonatologists prescribe iNO for the following reasons. First, it has been known for 2 decades that iNO rapidly increases oxygen saturations in many premature neonates.[4,35,36] This physiologic effect might be misconstrued as evidence that an iNO-exposed infant has "responded" to iNO therapy and thus may benefit from its continued use. Secondly, there is evidence that select subpopulations of extremely premature neonates might benefit from iNO therapy.[26,37] Although these patients comprise <5% of the overall premature population, it is conceivable that neonatologists extrapolate these hopeful outcomes to the care they provide patients with commoner presentations of RDS. Last,

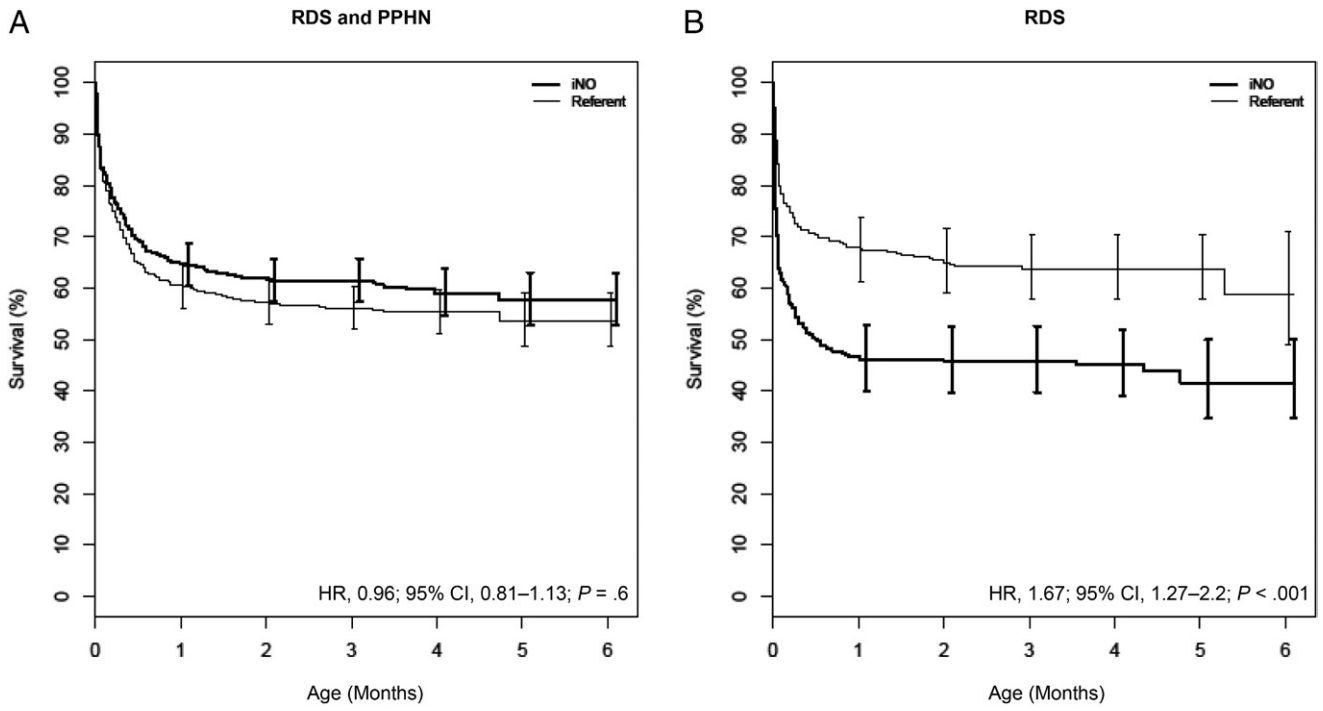

FIGURE 4

Overall survival by iNO status of (A) patients in the matched cohort with RDS and PPHN and (B) patients in the matched cohort with RDS. The survival estimates were derived from a Cox model, with patients entering the risk set at their respective age at the index date. The Cox model was adjusted for birth weight and prolonged ROM (RDS and PPHN) and for birth size and maximum support rating (RDS).

practicing neonatologists may not consider the results of the various RCTs[4–14] to be generalizable to their own practice or to a particular patient. Given the results of a meta-analysis of individual patient data,[17] we and others conclude that this seems unlikely.[38]

With this study, we also seem to refute that the outcomes of iNO clinical trials are not generalizable to the "real world" of US neonatology. To conduct our analyses, we employed data that were abstracted from the electronic health records of neonates hospitalized in >300 PMG NICUs across America and Puerto Rico. Thus, the subjects' demographics, neonatologists' clinical practices, and the resulting outcomes reflect the broad diversity of the US NICU experience. With this in mind, it is important to note that the subjects in our overall and matched cohorts were similar in gestational age, birth weight, sex, and race distribution to those included in the 2 largest US RCTs of early iNO.[9,12] Likewise, among subjects in our matched cohort, we observed a mortality rate intermediate to those observed in those trials and similar rates of bronchopulmonary dysplasia and CLD.[9,12]

We found that early iNO exposure was not associated with lower mortality among subjects whose RDS was accompanied by PPHN. This was not entirely surprising because PPHN in this population typically results from immaturity of the lung parenchyma rather than primary vascular pathology.[38] Still, it is important to acknowledge that the diagnosis of PPHN was entirely at the discretion of the PMG neonatologist, that is, there were no predetermined echocardiographic or bedside monitoring criteria required for diagnosis. That said, among the PPHN subcohort, the rates of echocardiographic examination were similar between the iNO-exposed group and the referents (48.7% and 48.7%, respectively), as were the rates of patent ductus arteriosus (73.4% and 78.2%, respectively). This would suggest that the subjects in each treatment group merited similar degrees of cardiovascular assessment and thus were as similar as would be expected after the matching process.

It was unexpected that early iNO exposure would be associated with higher mortality among subjects with RDS alone. In the absence of elevated pulmonary vascular pressures, iNO conceivably could promote left-to-right shunting through the patent ductus arteriosus and thus exacerbate pulmonary edema formation. When considering this finding and its implications,

we again must critically consider the validity of the PPHN diagnosis. By comparing the survival of referents in the RDS and PPHN and RDS subcohorts, we found higher mortality among those with the concomitant diagnosis of PPHN (HR, 1.49; 95% CI, 1.17–1.91; $P = .002$). Thus, despite similar baseline characteristics (Supplemental Table 3), the comorbid diagnosis of PPHN seemed to influence the outcome of early iNO treatment of RDS.

The quality of the data housed in the CDW is the chief strength of this study. We previously queried the same CDW tables to describe the rise in iNO use among neonates <34 weeks' gestation.[20,21] Among extremely premature neonates hospitalized in PMG NICUs, the rate of iNO use (6.2%) was similar to that of the Vermont Oxford Network (6.9%) and the New South Wales and Australian Capital Territory network (7.2%).[21,38] Given that 88.3% of our present study cohort were included in our previous studies and that the PMG experience with iNO seems generalizable,[38] it is possible to draw meaningful inferences from the above analyses.

CONCLUSIONS

Off-label prescription of iNO does not improve survival in extremely premature neonates with RDS. Neonates whose RDS is associated with PPHN have high rates of mortality and morbidity, neither of which is reduced by treatment with iNO in the first week of life. Among those without a concomitant diagnosis of PPHN, iNO therapy was associated with increased mortality.

ABBREVIATIONS

CDW: Clinical Data Warehouse
CGA: corrected gestational age
CI: confidence interval
CLD: chronic lung disease
HR: hazard ratio
iNO: inhaled nitric oxide
IQR: interquartile range
NEC: necrotizing enterocolitis
OR: odds ratio
PMG: Pediatrix Medical Group
PPHN: persistent pulmonary hypertension of the newborn
PS: propensity score
PVL: periventricular leukomalacia
RCT: randomized controlled trial
RDS: respiratory distress syndrome
ROM: rupture of membranes
ROP: retinopathy of prematurity
tROP: retinopathy of prematurity requiring treatment

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