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Addressing Teenage Tobacco Use: Still an Urgent Issue for Pediatricians

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Early Hypoxic Respiratory Failure in Extreme Prematurity: Mortality and Neurodevelopmental Outcomes

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abstract

OBJECTIVES: To evaluate the survival and neurodevelopmental impairment (NDI) in extremely low birth weight (ELBW) infants at 18 to 26 months with early hypoxemic respiratory failure (HRF). We also assessed whether African American infants with early HRF had improved outcomes after exposure to inhaled nitric oxide (iNO).

METHODS: ELBW infants ≤1000 g and gestational age ≤26 weeks with maximal oxygen ≥60% on either day 1 or day 3 were labeled as "early HRF" and born between 2007 and 2015 in the Neonatal Research Network were included. Using a propensity score regression model, we analyzed outcomes and effects of exposure to iNO overall and separately by race.

RESULTS: Among 7639 ELBW infants born ≤26 weeks, 22.7% had early HRF. Early HRF was associated with a mortality of 51.3%. The incidence of moderate-severe NDI among survivors was 41.2% at 18 to 26 months. Mortality among infants treated with iNO was 59.4%. Female sex (adjusted odds ratio [aOR]: 2.4, 95% confidence interval [CI]: 1.8–3.3), birth weight ≥720 g (aOR: 2.3, 95% CI: 1.7–3.1) and complete course of antenatal steroids (aOR: 1.6, 95% CI: 1.1–2.2) were associated with intact survival. African American infants had a similar incidence of early HRF (21.7% vs 23.3%) but lower exposure to iNO (16.4% vs 21.6%). Among infants with HRF exposed to iNO, intact survival (no death or NDI) was not significantly different between African American and other races (aOR: 1.5, 95% CI: 0.6–3.6).

CONCLUSIONS: Early HRF in infants ≤26 weeks' gestation is associated with high mortality and NDI at 18 to 26 months. Use of iNO did not decrease mortality or NDI. Outcomes following iNO exposure were not different in African American infants.

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WHAT'S KNOWN ON THIS SUBJECT: The incidence of early hypoxemic respiratory failure and inhaled nitric oxide therapy are common in preterm infants ≤26 weeks' gestation. There is limited information regarding developmental outcomes and survival at 18 to 26 months by race outside randomized trials.

WHAT THIS STUDY ADDS: In preterm infants ≤26 weeks' gestation, early hypoxemic respiratory failure is associated with high mortality and severe neurodevelopmental impairment among survivors at 18 to 26 months. Therapy with inhaled nitric oxide did not reduce mortality or severe neurodevelopmental impairment in preterm infants of all races.

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Surfactant therapy, advanced ventilation techniques, and continuous positive airway pressure have significantly reduced pulmonary morbidity in extremely preterm infants.[1] Despite these measures, some preterm infants continue to suffer from hypoxemic respiratory failure (HRF).[2] Some of these infants may have associated persistent pulmonary hypertension of newborn (PPHN).[3] Off-label use of inhaled nitric oxide (iNO) is not recommended in preterm infants.[4,5] However, newer guidelines from various societies recommend the selective use of iNO among preterm infants with HRF associated with PPHN physiology.[6–9] Limited data are available from randomized controlled trials (RCTs) to guide neonatal providers in counseling parents regarding the neurodevelopmental outcomes of HRF at ≤26 weeks' gestation in the first few postnatal days.[2,10] Observational studies demonstrate the widespread use of iNO for early HRF in the NICU[11,12] without any evidence of benefit, even among infants with PPHN. Also, iNO exposure was associated with higher mortality among preterm neonates whose respiratory distress syndrome (RDS) was not accompanied by PPHN even after adjusting for birth size and maximum support rating.[12] However, these studies do not include neurodevelopmental outcomes after discharge from the NICU.

A recent individual participant data meta-analysis suggests a significant reduction in the composite outcome of death or bronchopulmonary dysplasia (BPD) with iNO treatment among African American (AA) infants.[13] AA adults were found to have lower bioavailability of NO compared with white individuals, providing biological plausibility for a differential effect by race.[14,15] It is unknown if survival and long-term neurodevelopmental benefits are seen in infants with early HRF treated with iNO. Our primary objective was to report the 18- to 26-month outcomes of extremely low birth weight (ELBW) infants born at ≤26 weeks' gestation at birth with early HRF. We hypothesized that extremely preterm infants with early HRF would have higher morbidity, mortality, and neurodevelopmental impairment (NDI) at 18 to 26 months of age compared with those without HRF. We further hypothesized that iNO would not improve survival, BPD, or neurodevelopmental outcomes among ELBW infants with early HRF. Finally, we also hypothesized that ELBW infants with HRF whose parents self-reported as African American would have lower mortality, BPD, and NDI after exposure to iNO.[13,16]

METHODS

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Generic Database prospectively collects data on preterm infants with a birth weight (BW) of ≤1000 g and gestational age (GA) ≤26 weeks. Follow-up data on these infants at 18 to 26 months are available. These data are collected at each site after institutional review board approval. We included all infants born from January 1, 2007, to December 31, 2015.

Data on Early HRF

On day 1 and day 3, the maximum fraction of inspired oxygen (F_{IO_2}) was recorded. Infants whose maximal F_{IO_2} was ≥0.6 on either of these days were labeled as "early HRF."[17] Because higher inspired oxygen requirement is common on the day of birth (day 0) among preterm infants, we did not include maximal F_{IO_2} on that day in our definition of early HRF. Exposure to iNO during the neonatal period (first 28 days of postnatal age) was also collected.[8,18] BW, GA, sex, race, ethnicity, duration of rupture of membranes (ROM), Apgar scores, antenatal steroids (ANS), and maternal chorioamnionitis data were collected. A complete course of ANS was defined as a mother receiving 2 doses of steroids before delivery. The prolonged preterm rupture of membranes (PPROM) was defined as ROM for ≥18 hours before delivery. Infants with congenital anomalies and those treated with iNO after 28 days of life were excluded. We further analyzed a subgroup of infants with HRF whose mothers self-identified as African American and studied the effect of iNO exposure in this population.

Data on Discharge Outcomes

Clinical characteristics such as BPD defined by the oxygen reduction test,[19] patent ductus arteriosus (PDA), culture-positive sepsis (both early and late), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) were collected (definitions in Supplemental Materials).

Data on Outcomes at 18 to 22 Months

The early HRF group was analyzed for characteristics associated with survival at discharge and at 18 to 26 months follow-up. Outcomes at 18 to 26 months between infants exposed versus not exposed to iNO were evaluated. Neurodevelopmental assessments at the corrected age 18 to 22 months (for infants born January 1, 2007, through June 30, 2012) or corrected age 22 to 26 months (for infants born July 1, 2012, through December 31, 2015) were performed by certified examiners. The Bayley Scales of Infant Development 3 (Bayley-III) includes composite scores (mean of 100 and a SD of 15) for cognitive, language, and motor skills. Scores range from 55 to 145, with a lower score indicating a greater degree of delay.[20] A standardized neurosensory examination was also performed. The

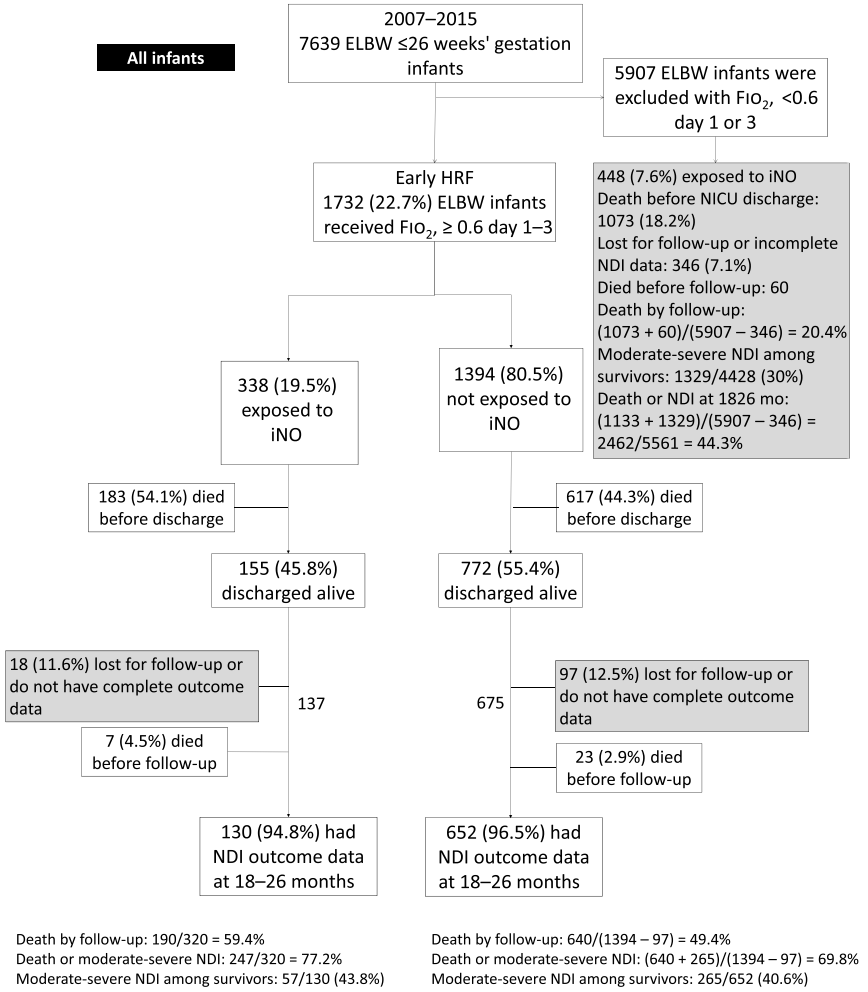

FIGURE 1
The flowchart of ELBW infants ≤26 weeks' gestation with early HRF.

severity of cerebral palsy was defined on the basis of the Gross Motor Function Classification System level, consisting of a scale from I (mild impairment) to V (severe impairment).[21,22]

For purposes of this analysis, the composite outcome of NDI consists of at least 1 of the following outcomes: moderate-severe cerebral palsy (Gross Motor Function Classification System level ≥II), a cognitive composite score of <85 on the Bayley-III, severe hearing loss (bilateral permanent hearing loss that interferes with the ability to understand or communicate with or without amplification), or severe visual impairment (no usable vision, usually defined as legally blind).[20]

Statistical Approach

Infant demographic and maternal characteristics were summarized and compared by using Student *t* test for continuous variables and χ^2 tests for categorical variables. Specifically, unadjusted comparisons of demographic and clinical outcomes between all infants with and without HRF were performed. Additionally, among infants with HRF, exposure to iNO versus no exposure was compared.

A multivariable logistic regression model was constructed to evaluate factors associated with early HRF. A propensity score to quantify the probability of receiving iNO therapy for each subject was created from a multivariable logistic regression model. The propensity scores were ranked and classified into similar groups on the basis of their ranks. Six groups were created that included infants with and without iNO. Subjects within each group had a similar probability of iNO treatment and were balanced on key covariates.[23,24] Separate multivariable logistic regression models were then constructed to identify factors associated with survival at discharge and intact survival at 18 to 26 months follow-up, adjusting for the propensity scores and other covariates.

A list of a priori risk factors was considered in all the initial models for propensity scores, risk factors for HRF, survival at discharge, and intact survival at follow-up. The list included the following variables: BW, GA, sex, ethnicity, duration of ROM, Apgar scores, ANS, maternal chorioamnionitis, delivery by cesarean delivery (small for gestational age [SGA]), birth centers, year of birth, and use of iNO. The PPROM and ANS were not correlated, and both the variables were considered in the model. Additionally, the groups based on the propensity scores were also considered as a covariate in both the models for survival at discharge and intact survival at follow-up models to even out any imbalance. The final model for each outcome was selected by using the backward elimination method, in which covariates with $P >$ .05 were dropped from the model. In the model for intact survival, PPROM was not significant but was added in the final model as a predefined clinically important factor.

Statistical interaction between PPROM and ANS was evaluated and was significant only in the model for survival at discharge. The interaction

TABLE 1 Characteristics of ELBW Infants ≤26 Weeks' Gestation With HRF

Characteristics	Early HRF, *n* = 1732	Infants Without Early HRF, *n* = 5907	*P*
Birth wt, g, mean ± SD	664.5 ± 144.9	727.9 ± 139.4	<.0001
GA, wk, mean ± SD	24.4 ± 1.1	24.8 ± 1.0	<.0001
Male sex, *n* (%)	946 of 1731 (54.7)	2889 of 5905 (48.9)	<.0001
Small for GA, *n* (%)	208 of 1731 (12.0)	371 of 5905 (6.3)	<.0001
PROM, *n* (%)			
>18 h	336 of 1683 (20.0)	1609 of 5745 (28.0)	<.0001
>24 h	289 of 1666 (17.3)	1419 of 5686 (25.0)	<.0001
>120 h	176 of 1668 (10.6)	753 of 5707 (13.2)	.0042
Race, *n* (%)			
AA	685 of 1732 (39.5)	2469 of 5907 (41.8)	.0947
White	722 of 1732 (41.7)	2226 of 5907 (37.7)	.0026
Hispanic	250 of 1732 (14.4)	864 of 5907 (14.6)	.8418
Other	63 of 1732 (3.6)	319 of 5907 (5.4)	.0031
Chorioamnionitis, *n* (%)	244 of 1716 (14.2)	1087 of 5872 (18.5)	<.0001
ANS, *n* (%)	983 of 1722 (57.1)	3926 of 5865 (66.9)	<.0001
Delivery by cesarean section, *n* (%)	1141 of 1729 (66.0)	3695 of 5904 (62.6)	.0097
Apgar scores <4 at 1 min, *n* (%)	1091 of 1714 (63.7)	2952 of 5864 (50.3)	<.0001
Apgar scores <4 at 5 min, *n* (%)	427 of 1716 (24.9)	886 of 5878 (15.1)	<.0001
BPD, traditional, *n* (%)	741 of 977 (75.8)	2867 of 4923 (58.2)	<.0001
BPD, physiologic definition, *n* (%)	713 of 971 (73.4)	2755 of 4883 (56.4)	<.0001
PDA, treatment and surgery, *n* (%)	899 of 1728 (52.0)	3143 of 5898 (53.3)	.3546
Postnatal steroid use for BPD, *n* (%)	347 of 1636 (21.2)	1050 of 5663 (18.5)	.0156
NEC stage II/III, *n* (%)	172 of 1731 (9.9)	722 of 5907 (12.2)	.0093
Early-onset sepsis, *n* (%)	59 of 1731 (3.4)	149 of 5902 (2.5)	.047
Late-onset of sepsis, *n* (%)	510 of 1504 (33.9)	1824 of 5730 (31.8)	.1251
ROP stage ≥III, *n* (%)	298 of 989 (30.1)	1062 of 4929 (21.5)	<.0001
Grade 3 or 4 IVH and PVL, *n* (%)	630 of 1614 (39.0)	942 of 5770 (16.3)	<.0001
Length of stay survivors, d, mean ± SD	132.9 ± 55.8	117.1 ± 46.2	<.0001
Mortality in the NICU, *n* (%)	800 of 1727 (46.3)	1073 of 5896 (18.2)	<.0001
18–26-mo outcomes among NICU survivors; neurodevelopment outcome of infants with or without HRF	*n* = 814	*n* = 4095	
Intact survival, no death or severe NDI, *n* (%)	460 of 812 (56.7)	2728 of 4090 (66.7)	<.0001
Death after NICU discharge, *n* (%)	30 of 814 (3.7)	60 of 4095 (1.5)	<.0001
Moderate-severe NDI, *n* (%)	322 of 782 (41.2)	1302 of 4030 (32.3)	<.0001
Cerebral palsy, *n* (%)	173 of 783 (22.1)	518 of 4032 (12.8)	<.0001
Moderate to severe cerebral palsy, *n* (%)	100 of 782 (12.8)	254 of 4032 (6.3)	<.0001
Bayley-III cognitive, mean ± SD	84.4 ± 16.7	88.2 ± 15.1	<.0001
Hearing impairment, *n* (%)	35 of 783 (4.5)	112 of 4028 (2.8)	.012
Vision impairment, *n* (%)	22 of 781 (2.8)	53 of 4032 (1.3)	.0019

effects between iNO and other covariates were evaluated and were not significant in any of the models and were excluded. Specifically, the interaction between iNO and AA race was not significant (P = .323). As a predefined secondary objective, subgroup analyses for only AA infants were performed, including an adjusted model for survival without physiologic BPD at discharge and intact survival at follow-up.

Model fit for all the logistic models were assessed by using Hosmer–Lemeshow test. The time of death in infants with and without HRF was compared by using the Kaplan-Meier curves. All reported P values are 2-sided and considered statistically significant at <.05. Analyses were performed with SAS/STAT software, Version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

During the period 2007 to 2015, there were 7639 ELBW infants born at ≤26 weeks' gestation within the NRN centers (Fig 1). A total of 1732 (23%) of these infants were exposed to ≥0.6 F_{IO_2} during days 1 and 3 and were labeled early HRF.

Characteristics and Outcome of Early HRF

ELBW infants with early HRF had lower BW, GA, and 5 min Apgar scores compared with infants without early HRF (Table 1). The incidence of PPROM and ANS was significantly lower in the early HRF group. Preterm infants with lower BW (<720 g), male sex, SGA, or delivery by cesarean were more likely to be associated with early HRF (Supplemental Table 6). The BW of 720 g was chosen as a cutoff after including weight as a continuous variable in the initial statistical analysis. Higher GA, maternal chorioamnionitis, PPROM, and ANS decreased the risk of HRF.

Thirty infants died after NICU discharge before follow-up (Fig 1). Of the 927 infants with early HRF discharged from the NICU, 115 (12.5%) infants were lost to follow-up or did not have complete data on neurodevelopmental outcomes available. The overall incidence of death (in-hospital plus postdischarge) and/or moderate-severe NDI in this population was 71.2% (1152 of 1617 patients). A nonresponse bias analysis to account for infants lost to follow-up was performed, and there was no significant difference in the characteristics other than the treatment of PDA, which was higher in the group with follow-up (Supplemental Table 7). Among 782 infants with complete follow-up data, 41.2% (322 of 782) had moderate-severe NDI. Among infants with early HRF, higher BW (≥720 g), higher GA, female sex, Apgar score >4 at 1 minute and at 5 minutes, prolonged rupture of membrane (PROM) >18 hours and/or ANS, and center were associated with increased survival to

TABLE 2 Factors Associated With Survival at Discharge With HRF

Factors Associated With Survival at Discharge in ELBW Infants With O_2 ≥ 60% on Day 1 and Day 3	*P*	aOR	95% CI	95% CI
Birth wt ≥720 g, yes versus no	<0.0001	2.028	1.567	2.623
GA	<0.0001	1.400	1.254	1.562
Female, yes versus no	0.0046	1.367	1.101	1.696
AA, yes versus no	0.0014	1.390	1.088	1.777
Apgar >4 at first minute, yes versus no	0.0085	1.291	1.009	1.652
Apgar >4 at fifth minute, yes versus no	0.0420	1.462	1.118	1.913
Not exposed to iNO, yes versus no	<0.0001	1.967	1.467	2.638
PROM >18 and ANS				
Both PROM and ANS versus No PROM or ANS	<0.0001	1.535	1.108	2.127
Only ANS versus No PROM or ANS	<0.0001	1.450	1.124	1.870
Only PROM versus No PROM or ANS	0.3401	1.261	0.692	2.298
Center variation	<0.0001	Differs with each center (Supplemental Table 8)	Differs with each center (Supplemental Table 8)	Differs with each center (Supplemental Table 8)

discharge from the NICU (Table 2). Exposure to iNO was associated with reduced survival to NICU discharge. Preterm infants ≤26 weeks with HRF had significantly lower survival probability compared with those without HRF as shown in Fig 2. ANS, higher BW (≥720 g), and female sex were associated with intact survival at 18 to 26 months (Table 3).

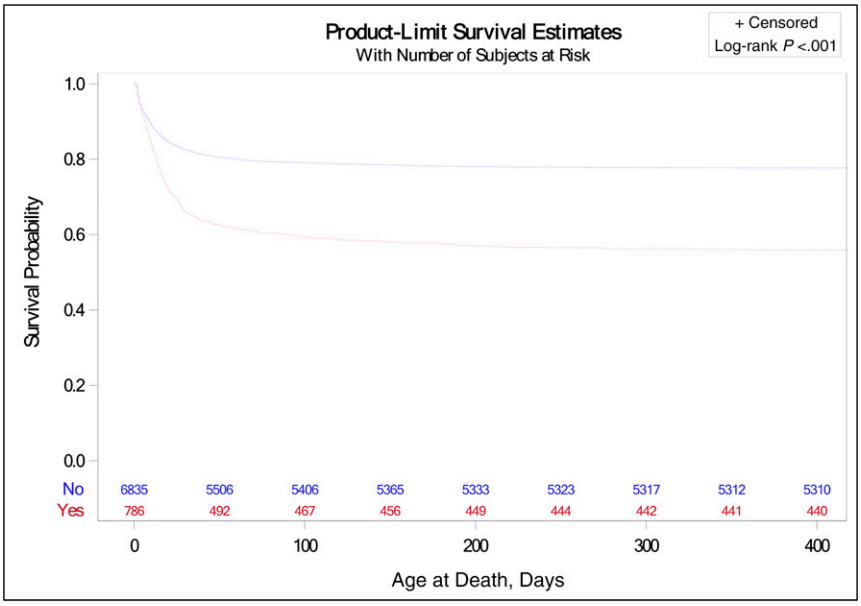

FIGURE 2
The Kaplan–Meier plot shows the probability of survival (y-axis) by days (x-axis), between infants with HRF (interrupted line) versus infants without HRF (continuous line).

Exposure to iNO and Outcomes in Early HRF

As expected, HRF was also associated with increased exposure to iNO, with considerable variation in exposure between centers. Extremely preterm infants with early HRF with the following characteristics were more likely to receive iNO: PPROM, ANS, Apgar score <4 at 1 minute, and birth in the year 2011 or after. There was a wide variation between centers regarding iNO use (range: 1%–38%, Supplemental Table 8). Characteristics of infants with early HRF based on exposure to iNO are shown in Table 4.

Exposure to iNO was associated with reduced survival to NICU discharge. Infants with early HRF exposed to iNO in the neonatal period had a higher rate of combined morbidities and in-hospital mortality of 54.1% compared with 44.4% in infants not exposed to iNO. There was no significant difference in survival when early HRF infants exposed to iNO were stratified on the basis of PPROM (Supplemental Table 9). In addition, when we compare infants with no PROM or PROM <120 hours, the survival is 118 of 251 = 47%, which is identical to survival of 45% with PROM >120 hours. The incidence of BPD, PDA requiring treatment, sepsis, length of stay, and mortality were higher with exposure to iNO among extremely preterm infants with HRF (Table 5). There was no difference in the incidence of grade 3 or 4 IVH and PVL (34.6% with iNO exposure vs 40.2% among infants not exposed to iNO, *P* = .0653). The incidence of morbidities such as cerebral palsy and hearing and vision impairment at discharge were not different among survivors with early HRF

TABLE 3 Factors Associated With Intact Survival at 18 to 26 Months

Factors Associated With Intact Survival at 18–26 mo in ELBW Infants With $O_2 \geq 60\%$ on Day 1 and Day 3	*P*	aOR	95% CI	95% CI
Birth wt ≥ 720 g, yes versus no	<0.0001	2.277	1.669	3.107
Female, yes versus no	<0.0001	2.427	1.789	3.293
PROM >18 hr	0.2134	0.999	0.999	1.000
Complete course of ANS, yes versus no	0.0082	1.551	1.120	2.147

exposed to iNO and not exposed to iNO (Table 5).

AA ELBW Infants

AA preterm infants had a similar incidence of early HRF (21.7% vs 23.3%) compared with other races (Fig 3). AA infants with HRF had a significantly lower rate (16.35%) of iNO use compared with other races (21.6%) ($P = .0072$). We did observe center variations in the use of iNO in AA infants. Two centers had higher rates of iNO use in AA infants when compared with other races, whereas 2 centers used less iNO (Supplemental Table 8). Overall, some centers with more AA infants used less iNO among all infants, accounting for differences in rates of iNO use (Supplemental Table 8). The number from each center and the decision to use iNO appears to be variable based on individual provider preference, center protocols and different interpretation of the literature. Among extremely preterm infants with early HRF exposed to iNO, there was no difference in the incidence of physiologic BPD among AAs (86.8%), as compared with infants of other races (94.1%, $P = .1$). Among AA infants with early HRF, 70% developed BPD compared with 50% without early HRF. There was no difference in BPD rates in AA infants with early HRF (70.1%) compared with other races (75.6%, $P = .056$).

Among all extremely preterm infants (with and without early HRF), AA infants had similar NICU mortality (25.4% vs 23.9%) but higher postdischarge mortality by 18 to 26 months (2.1% vs 1.1%). Adjusted analyses considering only AA infants revealed similar findings as the overall models for survival at discharge and intact survival at follow-up. AA infants overall had higher chances of survival compared with non-AA infants (adjusted odds ratio [aOR]: 1.4, 95% confidence interval [CI]: 1.09–1.8). However, within the AA population, death and NDI in infants with HRF was much higher (473 of 641: 89.3%) compared with those infants without HRF (1152 of 2198: 52.4%). Among HRF infants exposed to iNO, intact survival (no death or NDI) was not significantly different between AA and other races (aOR: 1.5, confidence interval: 0.6–3.6) (Supplemental Table 10). The AA infants who did not receive iNO had higher survival without physiologic BPD at discharge (aOR: 4.6, 95% confidence interval: 2.0–11.0). The mortality before discharge in this subgroup with HRF was 45.7%, as compared with 19% without HRF. For the AA subgroup, infants with BW >720 g and female sex had higher survival at discharge. Similarly, for the AA infants, the intact survival at follow-up was not significantly different for infants with and without iNO therapy.

TABLE 4 Baseline Characteristics of Infants With Early HRF Based on Exposure to iNO During the Neonatal Period

Characteristics	Exposed to iNO, *n* = 338	Not Exposed to iNO, *n* = 1394	*P*
Birth wt, g, mean ± SD	652.4 ± 150.8	667.5 ± 143.3	.085
GA, wk, mean ± SD	24.4 ± 1.2	24.4 ± 1.1	.8154
Male sex, *n* (%)	185 of 338 (54.7)	761 of 1393 (54.6)	.9727
Small for GA, *n* (%)	57 of 338 (16.9)	151 of 1393 (10.8)	.0022
ROM, *n* (%)			
>18 h	100 of 320 (31.3)	236 of 1363 (17.3)	<.0001
>24 h	88 of 314 (28.0)	201 of 1352 (14.9)	<.0001
>120 h	63 of 316 (19.9)	113 of 1352 (8.4)	<.0001
Race, *n* (%)			
AA	112 of 338 (33.1)	573 of 1394 (41.1)	.0072
White	167 of 338 (49.4)	555 of 1394 (39.8)	.0013
Hispanic	44 of 338 (13.0)	206 of 1394 (14.8)	.4088
Other	13 of 338 (3.8)	50 of 1394 (3.6)	.8193
Chorioamnionitis, *n* (%)	60 of 331 (18.1)	184 of 1385 (13.3)	.0235
ANS, *n* (%)	226 of 334 (67.7)	757 of 1388 (54.5)	<.0001
Delivery by cesarean, *n* (%)	231 of 337 (68.5)	910 of 1392 (65.4)	.27
Apgar scores <4 at 1 min, *n* (%)	231 of 334 (69.2)	860 of 1380 (62.3)	.0197
Apgar scores <4 at 5 min, *n.* (%)	91 of 334 (27.2)	336 of 1382 (24.3)	.2659

DISCUSSION

In our study, we focus on death or intact survival at follow-up as the primary outcome in preterm neonates ≤26 weeks' gestation with early HRF. Early HRF, as defined as a requirement of ≥60% oxygen on day 1 or day 3, was observed in 22.7% of ELBW infants born at ≤26 weeks' gestation in our study. A striking finding was that early HRF was associated with higher in-hospital mortality (46.2% vs 18.2%), postdischarge mortality (3.7% vs 1.3%) and severe NDI among survivors (41.2% vs 30%) compared with those without HRF.

TABLE 5 Outcomes of Infants With and Without Exposure to iNO in Infants With Early HRF

Characteristics	Exposed to iNO, *n* = 338	Not Exposed to iNO, *n* = 1394	*P*
BPD, traditional, *n* (%)	157 of 172 (91.3)	584 of 805 (72.5)	<.0001
BPD, physiologic definition, *n* (%)	157 of 171 (91.8)	556 of 800 (69.5)	<.0001
PDA, treatment and surgery, *n* (%)	202 of 337 (59.9)	697 of 1391 (50.1)	.0012
Postnatal steroid use for BPD, *n* (%)	107 of 324 (33.0)	240 of 1312 (18.3)	<.0001
NEC stage II/III, *n* (%)	27 of 338 (8.0)	145 of 1393 (10.4)	.182
Early-onset sepsis, *n* (%)	18 of 338 (5.3)	41 of 1393 (2.9)	.0304
Late-onset of sepsis, *n* (%)	124 of 312 (39.7)	386 of 1192 (32.4)	.0145
ROP stage ≥III, *n* (%)	63 of 178 (35.4)	235 of 811 (29.0)	.0911
Grade 3 or 4 IVH and PVL, *n* (%)	112 of 324 (34.6)	518 of 1290 (40.2)	.0653
Length of stay survivors, d, mean ± SD	150.8 ± 70.2	129.3 ± 51.8	<.0001
Mortality in the NICU, *n* (%)	183 of 338 (54.1)	617 of 1389 (44.4)	.0013
18–26 mo, characteristics among NICU survivors	*n* = 137	*n* = 677	
Intact survival, no death or severe NDI, *n* (%)	73 of 137 (53.3)	387 of 675 (57.3)	.3833
Death after NICU discharge, *n* (%)	7 of 137 (5.1)	23 of 677 (3.4)	.332
Moderate-severe NDI, *n* (%)	57 of 130 (43.8)	265 of 652 (40.6)	.4982
Cerebral palsy, *n* (%)	32 of 129 (24.8)	141 of 654 (21.6)	.4166
Moderate to severe cerebral palsy, *n* (%)	16 of 129 (12.4)	84 of 653 (12.9)	.8862
Bayley-III cognitive, mean ± SD	84.1 ± 17.4	84.4 ± 16.6	.8339
Hearing impairment, *n* (%)	7 of 130 (5.4)	28 of 653 (4.3)	.5805
Loss of vision, *n* (%)	3 of 129 (2.3)	19 of 652 (2.9)	.712

The association between early HRF and lower BW, GA, and male sex was expected given the higher association of RDS with these characteristics.[25] Interestingly, chorioamnionitis, PROM, and exposure to ANS were associated with lower incidence of early HRF. We speculate that chorioamnionitis and PROM are associated with exposure to inflammatory cytokines and acceleration of lung maturation and lower incidence of early HRF.[26] Similarly, exposure to ANS is associated with decreased incidence of RDS, acceleration of fetal lung maturation, along with decreased pulmonary vascular resistance and vasodilator response to nitric oxide and catecholamines.[27–29]

Despite formal recommendations against such use, almost one-fourth of extremely preterm infants with early HRF were exposed to iNO, with significant center variation.[4,5] Among infants with early HRF, factors such as race, SGA status, PPROM, chorioamnionitis, and ANS were associated with a higher incidence of exposure to iNO. These factors are likely associated with increased severity of HRF and/or associated pulmonary hypertension (PH). Also, PPROM can be associated with pulmonary hypoplasia and PH, resulting in therapy with iNO.[30] In our study, the survival of 45% in the cohort of infants with PPROM >120 hours may warrant further investigation of the use of iNO in this patient population. Although the duration of ROM was collected, we did not collect information about pulmonary hypoplasia or echocardiographic evidence of PH in our patients. Exposure to iNO was an independent factor associated with mortality at discharge, but no causality was identified. We speculate that the severity of illness is higher in the iNO-treated infants and the higher mortality reflect a "last-ditch effort" use in moribund preterm infants.

Infants exposed to iNO with early HRF had a higher incidence of BPD, PDA, sepsis, mortality, and postnatal steroid use, suggesting higher acuity in these patients. In contrast to the largest RCT in which researchers evaluated iNO for HRF in preterm neonates,[2] we observed a tendency toward a lower incidence of severe IVH and PVL in infants exposed to iNO with BW <750 g (P = .0503). Among survivors, iNO did not alter the rate of NDI. The incidence of death or NDI was high (75%) in the current study, and these rates are similar to those reported by Hintz et al[31] (87%) in an iNO group enrolled in the NRN trial with BW ≤1000 g). In contrast to the findings of Askie et al,[13] who examined prophylactic use of iNO for BPD prevention using individual patient data analysis (in preterm infants <34 weeks), we found that iNO has no impact on short- or long-term outcomes in extremely premature infants (≤26 weeks) with early HRF irrespective of race.[32] More recent evidence linking iNO exposure in the NICU to childhood cancer further emphasizes the need for the selective use of iNO among preterm infants with HRF[33] and the possible role of free radicals in carcinogenesis.[34]

This current analysis supports the National Institutes of Health Consensus Development Conference statement discouraging routine rescue therapy with iNO and emphasizes the need for further studies evaluating the selective use of iNO on the basis of risk of BPD, presence of pulmonary hypoplasia, race, or presence of PH.[3,7] The use of iNO among preterm infants continues to be high in the United States.[35,36] Authors of two editorials recently speculated that the persistent use of iNO in preterm infants is because clinicians feel that the evidence from RCTs cannot be generalized to individual clinical situations.[37,38] Similarly, researchers in three other studies have suggested

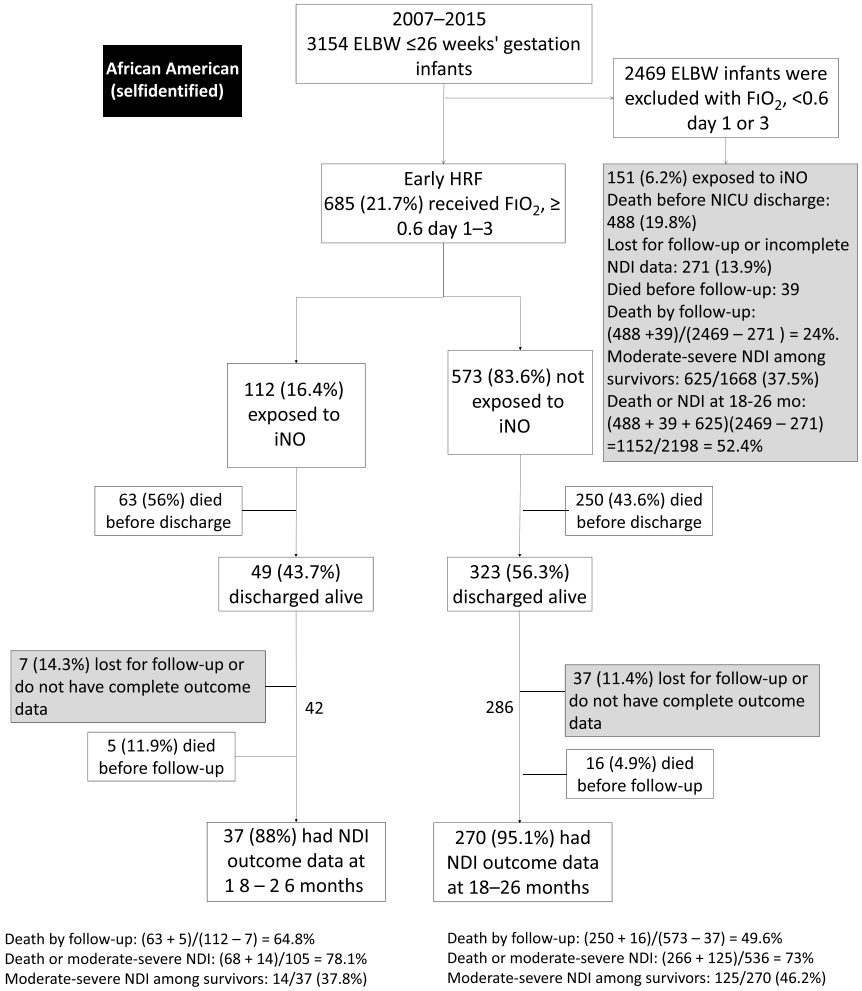

FIGURE 3
The flowchart of ELBW infants ≤26 weeks' gestation with early HRF whose mother self-identified as African American.

that iNO could be beneficial in preterm neonates if specific criteria are followed.[39–41] Providers' previous experience with iNO, the safety profile in term infants, and finally, a perception of offering patient-centered care with involvement of parents in shared decision-making all might also contribute to high iNO use among preterms with early HRF.[42] With our study, we provide additional evidence to support the findings of the NRN RCT, which enrolled critically ill ELBW infants with HRF.[2,31]

Authors of a recent individual participant data meta-analysis have shown a reduced incidence of BPD after iNO use among preterm infants, with the most significant effect in AA infants.[13] Our analysis did not include patient data from randomized trials and has the limitations of a retrospective analysis. However, it includes prospectively collected individual patient data from an established neonatal research network of academic institutions. We therefore evaluated our registry data from a geographically diverse multicenter network in the United States to see if extremely preterm AA infants with early HRF benefited from exposure to iNO. The mortality data for 2017 demonstrate a threefold difference in mortality rate from neonatal respiratory distress of newborn among non-Hispanic white race compared with non-Hispanic Black individuals (8.5 vs 24.1 per 100 000 live births).[43] The rate of mortality from chronic respiratory disease originating in the perinatal period was also significantly lower among non-Hispanic white compared with Black individuals (2.4 vs 8.5 per 100 000 live births).[43] In our study, among infants with early HRF, without adjusting for factors, the incidence of mortality and physiologic BPD were not different between the AA compared with the other races. We found no benefit in survival or neurodevelopmental outcome with iNO use. Regardless of the use of iNO, extremely preterm AA infants had lower trends of BPD (70.1% vs 75.6% among other races, $P = .056$). However, after exposure to iNO, no difference in the incidence of BPD was observed. Although the incidence of early HRF is similar among AA infants compared with other races (21.7% vs 23.3%), the use of iNO was significantly lower among them. This difference is related to center-differences in iNO use and differences in the proportion of AA infants. We cannot rule out differences in medication use based on race that has been observed in other studies or differing baseline HRF severity.[44] Further investigation to understand racial differences in resource use and higher post-NICU discharge mortality among AA preterm neonates is warranted.

Additional information on the cause of HRF, oxygenation, blood gas parameters, echocardiographic evidence of PH, oligohydramnios, pulmonary hypoplasia, and the time of initiation of iNO and response were not available and are significant limitations to this

analysis. Hence, we were unable to stratify and study the effects of iNO on patients with PH, pulmonary hypoplasia on mortality, and NDI. It is possible that a subgroup of patients with oligohydramnios, pulmonary hypoplasia, and PH pathophysiology may respond well to iNO as described previously.[8,30] We defined HRF on the basis of inspired oxygen requirements and did not have data on Pao_2 or Spo_2 to use the standard definition of HRF using oxygenation index. Finally, definition of race was based on maternal self-identification.[45] Furthermore, iNO exposure duration may be brief in some of these neonates, and although propensity modeling was done in these neonates, all confounding factors may not have been adjusted. Also, because most grade III/IV IVHs occur during the first 3 days of life, especially in infants with HRF, the exposure to iNO and IVH could be incidental.

There are several strengths to the current study. To our knowledge, this is the first study in which early HRF in extremely preterm infants ≤26 weeks was evaluated. Complete neurodevelopmental and mortality outcome data were available in 93.4% of the original cohort. To date, this is the largest study evaluating early HRF and iNO use in ELBW infants that includes neurodevelopmental outcomes. In combination with other published studies, these outcome data could be used to develop RCTs with improved targeting to specific high-risk groups.

CONCLUSIONS

Early HRF in ELBW infants at ≤26 weeks is associated with high morbidity and mortality during the NICU course. Inhaled NO use in this cohort was associated with higher mortality and did not improve neurodevelopmental outcomes at 18 to 26 months. More than three-fourths of ELBW infants with HRF receiving iNO died or had severe NDI at 18 to 26 months. The outcomes following iNO exposure were not different among AA infants. This prognostic information should be discussed with parents during shared-decision making before initiating iNO in ELBW infants with early HRF.[42]

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ABBREVIATIONS

AA: African American
ANS: antenatal steroid
aOR: adjusted odds ratio
BPD: bronchopulmonary dysplasia
BW: birth weight
ELBW: extremely low birth weight
GA: gestational age
HRF: hypoxemic respiratory failure
iNO: inhaled nitric oxide
IVH: intraventricular hemorrhage
NDI: neurodevelopmental impairment
NEC: necrotizing enterocolitis
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NRN: Neonatal Research Network
PDA: patent ductus arteriosus
PH: pulmonary hypertension
PPHN: persistent pulmonary hypertension of newborn
PPROM: prolonged preterm rupture of membranes
PROM: prolonged rupture of membranes
PVL: periventricular leukomalacia
RCT: randomized controlled trial
RDS: respiratory distress syndrome
ROM: rupture of membranes
ROP: retinopathy of prematurity
SGA: small for gestational age

Dr McGowan reviewed and interpreted the follow-up data and helped with supervision, and critical review; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial was registered at www.ClinicalTrials.gov (identifier NCT00063063).

Data Sharing: Data reported in this article may be requested through a data use agreement. Further details are available at https://neonatal.rti.org/index.cfm?fuseaction=DataRequest.Home.

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