# Morbidity of Persistent Pulmonary Hypertension of the Newborn in the First Year of Life

Martina A. Steurer, MD[1,2,3], Rebecca J. Baer, MPH[3,4], Scott Oltman, MS[2,3], Kelli K. Ryckman, PhD[5], Sky K. Feuer, PhD[3], Elizabeth Rogers, MD[1,3], Roberta L. Keller, MD[1], and Laura L. Jelliffe-Pawlowski, PhD[2,3]

**Objective** To assess postdischarge mortality and morbidity in infants diagnosed with different etiologies and severities of persistent pulmonary hypertension of the newborn (PPHN), and to identify risk factors for these adverse clinical outcomes.

**Study design** This was a population-based study using an administrative dataset linking birth and death certificates, hospital discharge and readmissions records from 2005 to 2012 in California. Cases were infants ≥34 weeks' gestational age with *International Classification of Diseases, 9th edition*, codes consistent with PPHN. The primary outcome was defined as postdischarge mortality or hospital readmission during the first year of life. Crude and adjusted risk ratio (aRR) with 95% CIs were calculated to quantify the risk for the primary outcome and to identify risk factors.

**Results** Infants with PPHN (n = 7847) had an aRR of 3.5 (95% CI, 3.3-3.7) for the primary outcome compared with infants without PPHN (n = 3 974 536), and infants with only mild PPHN (n = 2477) had an aRR of 2.2 (95% CI, 2.0-2.5). Infants with congenital diaphragmatic hernia as etiology for PPHN had an aRR of 8.6 (95% CI, 7.0-10.6) and infants with meconium aspiration syndrome had an aRR of 4.0 (95% CI, 3.6-4.4) compared with infants without PPHN. Hispanic ethnicity, small for gestational age, severe PPHN, and etiology of PPHN were risk factors for the primary outcome.

**Conclusions** The postdischarge morbidity burden of infants with PPHN is large. These findings extend to infants with mild PPHN and etiologies with pulmonary vascular changes that are thought to be short term and recoverable. These data could inform counseling of parents. *(J Pediatr 2019;213:58-65)*.

The hallmark of successful transition from the intrauterine to the postnatal circulation is a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow.[1,2] When the pulmonary vascular resistance fails to fall postnatally, persistent pulmonary hypertension of the newborn (PPHN) results. A number of disorders impair this transition and can cause PPHN. Although there may be overlap, the underlying pathophysiology of PPHN can be characterized as 1 of 3 types: (1) abnormally constricted pulmonary vasculature owing to lung parenchymal diseases such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), or sepsis/infection, (2) remodeled pulmonary vasculature, known as idiopathic PPHN, or (3) hypoplastic vasculature as seen in congenital diaphragmatic hernia (CDH) or other congenital anomalies of the respiratory system.[1,2]

In the modern era, the overall mortality of infants with PPHN has been reported to be 7%-15%.[3-6] However, given its heterogeneity, mortality and other clinical outcomes depend on the severity and etiology of PPHN. Some etiologies are associated with pulmonary vascular changes that are thought to be short term and recoverable, whereas other etiologies such as lung hypoplasia are considered to be long term. Similarly, comorbidities associated with some etiologies can contribute to early mortality (eg, multiorgan dysfunction associated with sepsis or neonatal encephalopathy associated with MAS), whereas anatomic and physiologic abnormalities associated with birth defects might have persistent effects on child health.

Although neonatal mortality and hospital course of infants with severe PPHN have been well-described,[4-6] less is known about the postdischarge mortality and morbidity burden of this condition. A few studies report on neurodevelopmental abnormalities, bronchodilator use and hospital readmissions beyond the neonatal period in infants with the most severe forms of PPHN.[7-11] However, outcomes beyond the neonatal period have not been evaluated on a population basis, included infants

| | |
|---|---|
| aRR | Adjusted risk ratio |
| CDH | Congenital diaphragmatic hernia |
| ED | Emergency department |
| ICD-9 | *International Classification of Diseases, 9th Revision, Clinical Modification* |
| MAS | Meconium aspiration syndrome |
| OSHPD | California Office of Statewide Health Planning and Development |
| PPHN | Persistent pulmonary hypertension of the newborn |
| RDS | Respiratory distress syndrome |
| RR | Risk ratio |

From the [1]Department of Pediatrics, [2]Department of Epidemiology and Biostatistics, and [3]California Preterm Birth Initiative, University of California San Francisco, San Francisco; the [4]Department of Pediatrics, University of California San Diego, La Jolla, CA; and the [5]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA

Funded by the California Preterm Birth Initiative. The authors declare no conflicts of interest.


https://doi.org/10.1016/j.jpeds.2019.06.053

with less severe PPHN, or have numbers large enough to investigate variability in postdischarge outcomes according to the etiology of PPHN. Thus, the aim of this study was to assess postdischarge mortality and morbidity, measured by readmission to the hospital during the first year of life, in term (≥37 weeks of gestation) and late preterm (34-36 weeks of gestation) infants diagnosed with different etiologies and severities of PPHN. We further sought to identify risk factors for these adverse clinical outcomes.

## Methods

The California Office of Statewide Health Planning and Development (OSHPD) maintains a database that includes detailed information on maternal and infant characteristics derived from hospital discharge records that are linked to birth and death certificates from birth to one year of age. Diagnosis and procedure codes are based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9). Gestational age, birth weight, demographic factors, and maternal diagnoses are also available. The database has been used in multiple studies examining birth and neonatal outcomes.[12-18]

The study population consisted of live born infants from January 2005 to December 2012. We built on our previously identified cohort assembled with data from 2007-2011.[19] For the prior study, we excluded 2005-2006 owing to the relatively high percentage of missing maternal variables needed to assess risk factors for incidence of PPHN. However, for the current study focusing on outcomes, we included data from those 2 years. Additionally, we were able to use a newer OSHPD dataset that included 2012 and provided better linkage of hospital, birth, and death records, leading to a higher number of cases and controls for 2007-2011.

We used the same methodology to identify cases with PPHN as in our prior study.[19] Briefly, we identified infants born at $\geq 34^{0/7}$ weeks of gestation with ICD-9 codes consistent with the diagnosis of PPHN (747.83 [persistent fetal circulation], 416.0 [primary pulmonary hypertension], or 416.8 [other secondary pulmonary hypertension]) present in the birth hospitalization. Birth hospitalization was defined as the hospitalization from birth to death or initial discharge home, whichever comes first. The birth hospitalization includes any transfer to another hospital, if present. We excluded infants with major congenital heart disease, but included infants with minor cardiac defects associated with the diagnosis of PPHN, or diagnosed in its evaluation (eg, ventricular septal defect, atrial septal defect, and patent ductus arteriosus; ICD-9 codes 745-747.4, except 7.45.4-.6, 747). The following 6 underlying causes of PPHN were identified using ICD-9 codes in a hierarchical manner[19]: CDH, other congenital anomalies of the respiratory system, MAS, infection/sepsis and RDS, and idiopathic. A list of all ICD-9 codes and details about the methodology can be found elsewhere.[19]

To assess postdischarge outcomes in this expanded cohort, we excluded infants who died during the birth hospitalization. Our primary outcome was postdischarge mortality or any hospital readmission within the first year of life. The method of death ascertainment was death certificate or hospital discharge status of death for 2007-2011 and hospital discharge status of death for 2012. The OSHPD file contains stacked infant birth records and any other admissions or emergency department (ED) visits during their first year of life. Individuals in the file have a record identifier (birth ID) for birth records, hospital admissions, and ED visits. Infant transfers were identified when the discharge status of the infant indicated a discharge to another hospital. The subsequent row with an identical date of discharge and date of admission was presumed to be transfer record. Hospital admissions after initial discharge home or to a home health service were identified as readmissions. When an infant had an ED record with the same date as a hospital admission, only the hospital admission was used for the analyses. Our secondary outcomes were hospital readmission for respiratory cause, ED visit, and ED visit for respiratory cause. We defined respiratory cause as the presence of one of the following ICD-9 codes in the respective hospital readmission or ED visit record: acute respiratory infections including bronchiolitis (460-466), pneumonia and influenza (480-488), other diseases of upper respiratory tract (470-478), bronchitis (490-491), asthma (493), bronchiectasis (494), extrinsic allergic alveolitis (495), chronic airway obstruction (496), respiratory conditions owing to other and unspecified external agents (508), abscess of lung and mediastinum (513), other disease of lung (518.8), and other or unspecified disease of respiratory system (519.8 and 519.9).

We defined severe PPHN as the requirement for invasive or noninvasive positive pressure ventilation (ICD-9 diagnostic codes V46.1, V46.11, V46.12, V46.13, V46.14 and procedure codes 96.04, 96.70, 96.71, 96.72, 93.90, 93.91) in the birth hospitalization record. Infants without a code for positive pressure ventilation were classified as mild PPHN.

For the statistical analysis plan, we compared baseline characteristics for infants with and without PPHN by the $\chi^2$ test. We calculated crude risk ratios (RR) and adjusted RRs (aRR) and 95% CI for each outcome comparing infants with PPHN with infants without PPHN. We adjusted for gestational age, sex, birth weight (small for gestational age, adequate for gestational age, and large for gestational age) and race/ethnicity. We then calculated crude and aRR for each outcome separately in cases with severe and mild PPHN. Given the heterogeneity of underlying etiologies for PPHN, we compared primary and secondary outcomes in each etiology group of infants with PPHN with infants without PPHN calculating crude and aRR and 95% CI. Kaplan-Meier curves were generated to compare the primary outcome by underlying etiology of PPHN; crude hazard ratios with 95% CI were calculated. Finally, we calculated crude and aRR with 95% CI to identify risk factors associated with the primary outcome in infants with PPHN. All factors

significant in the univariate analysis were included in the multivariable model. A $P$ value of less than .05 was considered significant for all analyses. All analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina). The study protocol was approved by the institutional review board of the Health and Human Services Agency of the State of California.

## Results

Out of 3 974 536 infants, we identified 7847 infants with PPHN (incidence of 0.2%). Of all infants with PPHN, 68.4% (5370/7847) received invasive or noninvasive positive pressure ventilation meeting our criteria for severe PPHN; this was very similar to our previously described cohort (67.6%).[19] The distribution of etiologies of PPHN and infant characteristics were also similar to those we previously described[19] (**Table I**; available at www.jpeds.com). The most common etiology was infection (33.1%) followed by MAS (20.7%), idiopathic (20.3%), RDS (8.4%), other (7.0%), CDH (6.0%), and other anomalies of the respiratory system (4.5%). Infants with PPHN were more likely to be born prematurely (18.1% vs 7.0%; $P < .001$), to be small for gestational age (13.5% vs 9.4%; $P < .001$), and to be large for gestational age (17.9% vs 10.2%; $P < .001$).

The overall mortality in infants with PPHN was 7.3%, with a predischarge mortality of 6.5% and a 1-year postdischarge mortality of 0.7%. Of all infants with PPHN who survived to discharge, 28.6% were readmitted to the hospital at least once during their first year of life (compared with 9.8% of infants without PPHN; $P < .001$; **Table II**). About one-third of the hospital readmissions were for a respiratory cause in both infants with and without PPHN (10.4% readmission rate for respiratory cause in infants with PPHN and 3.4% in infants without; $P < .001$; **Table II**).

Our primary composite outcome of postdischarge mortality or any hospital readmission in the first year of life occurred in 29% of infants with PPHN vs 9.9% in infants without PPHN (crude RR and aRR of 3.7 [95% CI, 3.5-3.9] and 3.5 [95% CI, 3.3-3.7], respectively; **Table II**). The primary outcome occurred in 33.4% of infants with severe PPHN vs 9.9% of infants without PPHN (crude RR and aRR of 4.5 [95% CI, 4.3-4.8] and 4.2 [95% CI, 4.0-4.5], respectively; **Table III**, available at www.jpeds.com), and in 20.2% of infants with mild PPHN (crude RR and aRR of 2.3 [95% CI, 2.1-2.5] and 2.2 [95% CI, 2.0-2.5], respectively; **Table IV**, available at www.jpeds.com). Other secondary outcomes (ED visits and ED visits for respiratory cause) are presented in **Table II** for the entire group with PPHN, and in **Tables III** and **IV** for the subgroup of infants with severe and mild PPHN, respectively. **Table V** (available at www.jpeds.com) shows yearly rates of selected outcomes. Our primary outcome decreased from 32.2% in 2005 to 24.4% in 2012 ($P < .001$).

**Figure 1** shows the aRRs for selected outcomes according to PPHN etiology. For postdischarge mortality or hospital readmission (primary outcome; **Figure 1**), infants with anomalies of the respiratory system and CDH had the highest aRR with 14.0 (95% CI, 10.8-18.1) and 8.2 (95% CI, 6.7-10.2), respectively. We noted that the average initial hospitalization was approximately 60 days longer for these 2 groups, limiting the opportunity for primary outcome by 1 year of age. Infants with MAS, infection, and other etiologies of PPHN had initial hospitalizations that were

**Table II. Mortality, readmissions, or ED visits in first year of life in cases and controls**

| Characteristics | PPHN, n (%) | No PPHN, n (%) | Crude RR (95% CI) | aRR* (95% CI) |
|---|---|---|---|---|
| Entire sample | 7847 | 3 966 689 | | |
| Mortality | | | | |
| No | 7276 (92.7) | 3 960 260 (99.8) | Reference | Reference |
| Yes | 571 (7.3) | 6429 (0.2) | 44.5 (40.8-48.4) | 39.5 (36.2-43.1) |
| Predischarge mortality | 513 (6.5) | 2366 (0.1) | 97.2 (88.8-106.3) | 82.9 (75.5-91.1) |
| Postdischarge mortality | 58 (0.7) | 4063 (0.1) | 7.7 (5.9-9.9) | 7.2 (5.5-9.3) |
| Sample who survived to discharge | 7334 | 3 964 241 | | |
| Readmission | | | | |
| None | 5238 (71.4) | 3 574 165 (90.2) | Reference | Reference |
| Any | 2096 (28.6) | 390 158 (9.8) | 3.7 (3.5-3.8) | 3.5 (3.3-3.6) |
| >1 readmission | 426 (5.8) | 46 190 (1.2) | 6.2 (5.7-6.9) | 5.7 (5.2-6.3) |
| Readmission for respiratory cause | | | | |
| None | 6568 (89.6) | 3 827 826 (96.6) | Reference | Reference |
| Any | 766 (10.4) | 136 497 (3.4) | 3.3 (3.0-3.5) | 3.1 (2.9-3.3) |
| >1 readmission for respiratory cause | 151 (2.1) | 11 971 (0.3) | 7.3 (6.2-8.5) | 6.7 (5.7-7.9) |
| ED visits | | | | |
| None | 4688 (63.9) | 2 589 817 (65.3) | Reference | Reference |
| Any | 2646 (36.1) | 1 374 506 (34.7) | 1.1 (1.1-1.1) | 1.0 (1.0-1.1) |
| >1 ED visit | 1248 (17.0) | 595 024 (15.0) | 1.2 (1.1-1.2) | 1.1 (1.1-1.2) |
| ED visits for respiratory cause | | | | |
| None | 5940 (81.0) | 3 289 313 (83.0) | Reference | Reference |
| Any | 1394 (19.0) | 675 010 (17.0) | 1.1 (1.1-1.2) | 1.1 (1.1-1.2) |
| >1 ED visit for respiratory cause | 458 (6.2) | 186 850 (4.7) | 1.4 (1.2-1.5) | 1.3 (1.2-1.4) |
| Postdischarge mortality or hospital readmission | | | | |
| No | 5210 (71.0) | 3 571 569 (90.1) | Reference | Reference |
| Yes | 2124 (29.0) | 392 754 (9.9) | 3.7 (3.5-3.9) | 3.5 (3.3-3.7) |

*Adjusted for gestational age, sex, fetal growth, and race/ethnicity.

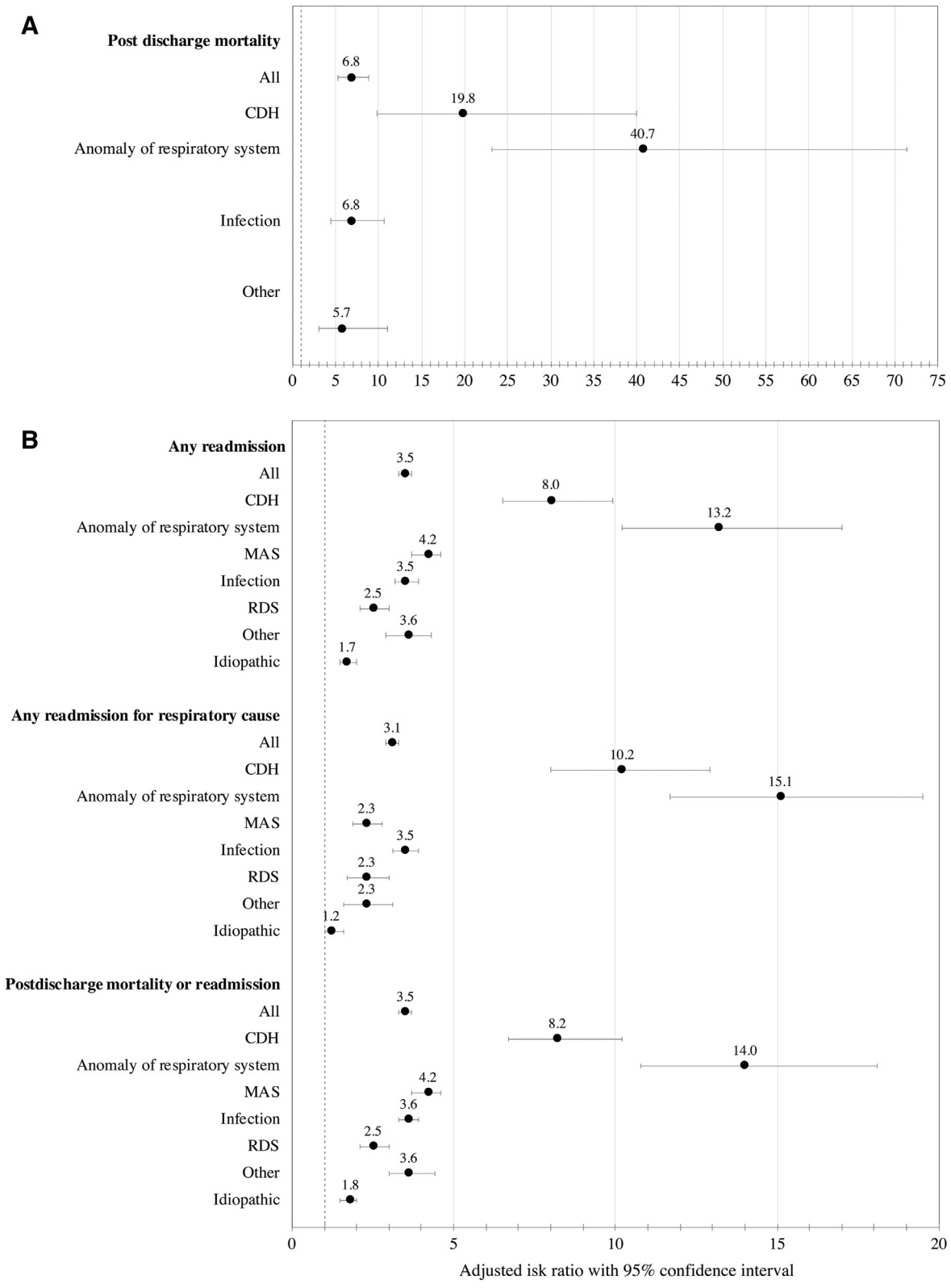


**Figure 1.** Forest plot for selected outcomes by etiology of PPHN compared to infants without PPHN. A, Post discharge mortality; B, Other selected outcomes in the first year of life. Adjusted Risk ratio: adjusted for gestational age, sex, birth weight and race/ethnicity. For post-discharge mortality, adjusted risk ratio not available for MAS, RDS or other due to the small number of postdischarge deaths in these groups. CDH = congenital diaphragmatic hernia (n = 470) , MAS = meconium aspiration syndrome (n = 1628), pulmonary anomaly (n = 352), infection (n = 2598), RDS = respiratory distress syndrome (n = 660), other = birth asphyxia, cystic kidney disease, hydrops fetalis, interstitial emphysema, leukemia, polycythemia, renal agenesis and dysgenesis, trisomy 21 (n = 547) and idiopathic (n = 1592).

**Table VI. Timing of mortality and readmissions in first year of life**

| Variables | All PPHN | CDH | Pulmonary anomaly | MAS | Infection | RDS | Other | Idiopathic |
|---|---|---|---|---|---|---|---|---|
| Entire sample | 7847 | 470 | 352 | 1628 | 2598 | 660 | 547 | 1592 |
| Mortality, n (%) | 571 (7.3) | 130 (27.7) | 112 (31.8) | 59 (3.6) | 149 (5.7) | 30 (4.6) | 39 (7.1) | 52 (3.3) |
| Age at death in days, median (IQR) | 8 (29) | 19 (39) | 4 (30.5) | 5 (24) | 7.5 (32) | 6 (27) | 5 (11) | 9.5 (51) |
| Any readmission, n (%) | 2096 (28.6) | 166 (47.7) | 154 (60.9) | 476 (30.3) | 740 (30.0) | 158 (25.0) | 148 (29.0) | 254 (16.4) |
| Age at first readmission in days, median (IQR) | 38 (122.5) | 59 (130) | 68.5 (168) | 14 (50) | 27 (97) | 39 (116) | 103.5 (151) | 80.5 (161) |
| Any readmission for respiratory cause, n (%) | 766 (10.4) | 96 (27.6) | 93 (36.8) | 117 (7.4) | 297 (12.0) | 56 (8.9) | 40 (7.8) | 67 (4.3) |
| Age at first readmission for respiratory cause in days, median (IQR) | 96 (156) | 106 (152) | 96 (142) | 71 (159) | 93.5 (166) | 86 (135.5) | 112.5 (150) | 93 (151.5) |

prolonged by 18-20 days compared with infants without PPHN. The aRR for the primary outcome for MAS was highest at 4.2 (95% CI, 3.7-4.6) and lowest for idiopathic PPHN (aRR, 1.8; 95% CI, 1.5-2.0). Table VI shows age at the primary outcome for each underlying cause of PPHN. Survival curves for the different underlying etiologies of PPHN are shown in Figure 2 (available at www.jpeds.com), demonstrating that infants with PPHN owing to CDH and other congenital pulmonary anomalies have new events extending into the latter part of their first year of life.

Table VII shows risk factors associated with our primary outcome. In the adjusted analysis, which included all variables significant in the univariate analysis, the only risk factors significantly associated with our primary outcome of postnatal discharge or at least one hospital readmission within the first year of life were Hispanic ethnicity (aRR, 1.2; 95% CI, 1.1-1.4), small for gestational age (aRR, 1.2; 95% CI, 1.1-1.3), severity of PPHN (aRR, 1.6; 95% CI, 1.5-1.8 for severe vs mild PPHN), and etiology of PPHN (Table VII). Table VIII shows mortality, readmission and ED visits infirst year of life in cases and controls without chromosomal anomalies or any congenital heart disease.

## Discussion

This contemporary, large, population-based cohort study assessed postdischarge mortality and morbidity burden measured by hospital readmissions during the first year of life in late preterm and term infants with different etiologies and severities of PPHN born in California. After adjusting for gestational age and other demographic variables, we found a >3-fold higher rate of postdischarge mortality or hospital readmission in infants with PPHN during the first year of life compared with infants without PPHN. Infants with severe PPHN, CDH, or pulmonary anomalies had the highest readmission rates. However, even infants with only mild PPHN or etiologies that are assumed to be short term, such as MAS, sepsis, or RDS, had a significantly increased hospital readmission rates compared with infants without PPHN. Finally, we identified severity and etiology of PPHN, Hispanic ethnicity, and small for gestational age as independent significant risk factors for postdischarge mortality and morbidity burden in the first year of life, but not gestational age.

There are few studies to date addressing morbidity and postdischarge mortality, and the data have been limited to infants with severe forms of PPHN.[7-10] For example, studies investigating the effect of inhaled nitric oxide on neonatal mortality reported hospital readmission rates from 20% to 39% at 1-4 years of age.[7-10] These figures are comparable with our hospital readmission rate of 32.9% in infants with severe PPHN. We found a readmission rate of 20% in the subgroup of infants with mild PPHN, which was twice as high as in infants without PPHN.

We also assessed rehospitalization rates for respiratory causes. The UK Collaborative ECMO Group studied severe PPHN, defined as an oxygenation index of >40. They reported 57 respiratory readmissions to the hospital in 99 infants during the first year of life without specifying how many infants were admitted multiple times.[11] In the present study, only about 30% of all readmissions were related to a respiratory cause, which was observed for the entire PPHN cohort with PPHN and for the severe and mild subgroups. It is possible that this was due to incomplete ICD-9 coding and that the true readmission rate for respiratory cause is somewhat higher. However, our findings demonstrate that PPHN is associated with other healthcare problems, and that a narrow focus exclusively on the respiratory status of these infants might omit the full extent of the morbidity burden.

In addition to the degree of severity, the underlying etiology of PPHN is an important determinant of clinical course and outcomes.[19] Generally, conditions that are associated with hypoplastic vasculature are severe and often lead to persistent PH. For example, the hospital discharge mortality for infants with CDH in the modern era is 30%-50% in population-based studies.[20,21] Burgos et al report a postdischarge mortality of 5% in 250 infants with CDH ≤2 years of age, with earlier deaths mainly owing to respiratory insufficiency and later deaths related to gastrointestinal morbidity.[22] In a prospective multicenter study, Wynn et al found that children with CDH scored significantly below the normal mean on the Bayley Scale of Infant Development-III motor, cognitive, and language domains at 2 years of age.[23] In our study, we confirm the high mortality and morbidity burden in this subgroup of infants. We found a postdischarge mortality of 1.7% in infants with CDH and 3.7% in infants with other anomalies of the respiratory system; these groups also had the highest percentage of hospital readmissions (47.7% and 60.9%, respectively).

The literature on mortality and morbidity burden in infants with PPHN owing to MAS, RDS, or infection is

**Table VII. Risk factors associated with postdischarge mortality or hospital readmissions in infants with PPHN**

| Variables | No mortality or hospital readmissions | Postdischarge mortality or hospital readmissions | Crude RR (95% CI) | aRR* (95% CI) |
|---|---|---|---|---|
| Sample | 5210 | 2124 | | |
| Gestational age (weeks) | | | | |
| 34-36 | 890 (17.1) | 381 (17.9) | 1.1 (0.9-1.2) | 1.1 (0.9-1.2) |
| 37-38 | 1524 (29.3) | 676 (31.8) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| 39-40 | 1189 (22.8) | 471 (22.2) | Reference | Reference |
| ≥41 | 601 (11.5) | 220 (10.4) | 0.9 (0.8-1.1) | 0.9 (0.8-1.1) |
| Sex | | | | |
| Male | 3011 (57.8) | 1284 (60.4) | Reference | Reference |
| Female | 2199 (42.2) | 840 (39.6) | 0.9 (0.8-1.0) | 0.9 (0.9-1.0) |
| Race | | | | |
| White not Hispanic | 1621 (31.1) | 582 (27.4) | Reference | Reference |
| Hispanic | 2095 (40.2) | 989 (46.6) | 1.2 (1.1-1.3) | 1.2 (1.1-1.4) |
| Black | 462 (8.9) | 197 (9.3) | 1.1 (1.0-1.3) | 1.1 (1.0-1.3) |
| Asian | 611 (11.7) | 213 (10.0) | 1.0 (0.8-1.1) | 1.0 (0.8-1.1) |
| Other | 421 (8.1) | 143 (6.7) | 1.0 (0.8-1.2) | 1.0 (0.8-1.2) |
| Birth weight† | | | | |
| Adequate for gestational age | 3588 (68.9) | 1471 (69.2) | Reference | Reference |
| Small for gestational age | 575 (11.0) | 305 (14.4) | 1.2 (1.1-1.3) | 1.2 (1.1-1.3) |
| Large for gestational age | 1028 (19.7) | 341 (16.1) | 0.9 (0.8-1.0) | 0.9 (0.8-1.0) |
| Maternal asthma | | | | |
| No | 4926 (94.6) | 1999 (94.1) | Reference | Reference |
| Yes | 284 (5.5) | 125 (5.9) | 1.1 (0.9-1.3) | 1.1 (0.9-1.3) |
| Smoking during pregnancy | | | | |
| No | 4911 (94.3) | 2011 (94.7) | Reference | Reference |
| Yes | 299 (5.7) | 113 (5.3) | 0.9 (0.8-1.1) | 0.9 (0.8-1.1) |
| Maternal age (years) | | | | |
| <18 | 90 (1.7) | 52 (2.5) | 1.3 (1.0-1.7) | 1.3 (1.0-1.7) |
| 18-34 | 3997 (76.7) | 1572 (74.0) | Reference | Reference |
| >34 | 1123 (21.6) | 500 (23.5) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| Maternal BMI‡ | | | | |
| Underweight | 104 (2.0) | 52 (2.5) | 1.2 (0.9-1.6) | 1.2 (0.9-1.6) |
| Normal weight | 1482 (28.5) | 554 (26.1) | Reference | Reference |
| Overweight | 916 (17.6) | 369 (17.4) | 1.1 (0.9-1.2) | 1.1 (0.9-1.2) |
| Obese | 1055 (20.3) | 403 (19.0) | 1.0 (0.9-1.2) | 1.0 (0.9-1.2) |
| Maternal diabetes | | | | |
| None | 4367 (83.8) | 1806 (85.0) | Reference | Reference |
| Preexisting | 175 (3.4) | 49 (2.3) | 0.7 (0.6-1.0)‡ | 0.8 (0.6-1.0) |
| Gestational | 668 (12.8) | 269 (12.7) | 1.0 (0.9-1.1) | 1.0 (0.9-1.2) |
| Mental illness | | | | |
| No | 4899 (94.0) | 2006 (94.4) | Reference | Reference |
| Yes | 311 (6.0) | 118 (5.6) | 0.9 (0.8-1.1) | 0.9 (0.8-1.1) |
| Illicit drug use | | | | |
| No | 5029 (96.5) | 2060 (97.0) | Reference | Reference |
| Yes | 181 (3.5) | 64 (3.0) | 0.9 (0.7-1.2) | 0.9 (0.7-1.2) |
| Hypertension | | | | |
| None | 4584 (88.0) | 1879 (88.5) | Reference | Reference |
| Preexisting | 114 (2.2) | 37 (1.7) | 0.8 (0.6-1.2) | 0.9 (0.6-1.2) |
| Gestational | 129 (2.5) | 59 (2.8) | 1.1 (0.8-1.4) | 1.1 (0.8-1.4) |
| Preeclampsia | | | | |
| No | 4889 (93.8) | 1997 (94.0) | Reference | Reference |
| Yes | 321 (6.2) | 127 (6.0) | 1.0 (0.8-1.2) | 1.0 (0.8-1.1) |
| Parity | | | | |
| Nulliparous | 2161 (41.5) | 827 (38.9) | 0.9 (0.9-1.0) | 0.9 (0.8-1.0) |
| Multiparous | 3046 (58.5) | 1296 (61.0) | Reference | Reference |
| Gestation | | | | |
| Singleton | 5080 (97.5) | 2087 (98.3) | Reference | Reference |
| Multiple | 130 (2.5) | 37 (1.7) | 0.8 (0.5-1.1) | 0.7 (0.5-0.9) |
| Maternal education (years) | | | | |
| <12 | 1218 (23.4) | 588 (27.7) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| 12 | 1350 (25.9) | 585 (27.5) | Reference | Reference |
| >12 | 2433 (46.7) | 863 (40.6) | 0.9 (0.8-1.0) | 0.9 (0.8-1.0) |
| Insurance | | | | |
| Private | 2243 (46.9) | 923 (43.5) | Reference | Reference |
| Public | 2472 (47.5) | 1089 (51.3) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| Self-pay | 107 (2.1) | 37 (1.7) | 0.9 (0.7-1.3) | 0.9 (0.7-1.3) |
| Other | 170 (3.3) | 69 (3.3) | 1.1 (0.8-1.3) | 1.0 (0.8-1.3) |

(*continued*)

**Table VII. Continued**

| Variables | No mortality or hospital readmissions | Postdischarge mortality or hospital readmissions | Crude RR (95% CI) | aRR* (95% CI) |
|---|---|---|---|---|
| FIPS code | | | | |
| 1-2 (urban) | 2693 (51.7) | 1137 (53.5) | Reference | Reference |
| 3-4 (moderately rural) | 770 (14.8) | 314 (14.8) | 1.0 (0.9-1.1) | 1.0 (0.9-1.1) |
| 5-6 (rural) | 57 (1.1) | 20 (0.9) | 0.9 (0.6-1.4) | 0.9 (0.5-1.3) |
| Type PPHN | | | | |
| Mild | 1961 (37.6) | 497 (23.4) | Reference | Reference |
| Severe | 3249 (62.4) | 1627 (76.6) | 1.7 (1.5-1.8) | 1.6 (1.5-1.8) |
| Etiology of PPHN | | | | |
| Idiopathic | 1289 (24.7) | 260 (12.2) | Reference | Reference |
| CDH | 179 (3.4) | 169 (8.0) | 2.9 (2.4-3.5) | 2.8 (2.3-3.4) |
| Congenital pulmonary anomaly | 95 (1.8) | 158 (7.4) | 3.7 (3.1-4.5) | 3.6 (2.9-4.4) |
| MAS | 1094 (21.0) | 478 (22.5) | 1.8 (1.6-2.1) | 1.9 (1.6-2.2) |
| Infection | 1720 (33.0) | 749 (35.3) | 1.8 (1.6-2.1) | 1.8 (1.5-2.0) |
| RDS | 473 (9.1) | 160 (7.5) | 1.5 (1.2-1.8) | 1.4 (1.1-1.7) |
| Other | 473 (9.1) | 160 (7.5) | 1.8 (1.4-2.1) | 1.7 (1.4-2.1) |

*BMI*, body mass index; *FIPS*, Federal Information Processing Standards.
*Adjusted for all significant predictors the univariate analysis.
†Definition according to Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. Pediatrics. 2014;133:844-853.
‡Underweight: BMI < 18.5 kg/m$^2$; normal weight: BMI 18.5-24.9 kg/m$^2$; overweight: BMI 25.0-29.9 kg/m$^2$; obese: BMI ≥ 30.0 kg/m$^2$.

scarce, possibly because pulmonary vascular disease is regarded as short term and recoverable. We found that infants with MAS, infection, and RDS had a significantly higher risk for readmission during the first year of life vs those without PPHN (Table VI). A greater percentage of these readmissions was due to nonrespiratory causes, underscoring the potential sequelae of multiorgan involvement.

Our findings have important implications for outpatient follow-up, counseling of parents, and preventive measures such as vaccinations. Further studies should investigate these clinical outcomes prospectively in infants with mild PPHN and etiologies such as MAS, RDS, or sepsis.

Aside from the severity and etiology of PPHN, we identified Hispanic ethnicity as a risk factor for postdischarge mortality or readmission. Although we previously reported that infants of Hispanic ethnicity were less likely to suffer from PPHN, our current findings show that after a diagnosis of PPHN, they are at higher risk for later adverse outcomes.[19] This finding was true after adjusting for sociodemographic risk factors such as maternal education or insurance status, pointing toward potential underlying biological variations. We also identified small for gestational age, a surrogate marker of fetal growth, as an independent risk factor for the primary outcome in this study. We previously identified small for gestational age as a risk factor for the incidence of PPHN, and we speculated that this association is potentially related to decreased pulmonary alveolar and vessel growth or pulmonary artery endothelial cell dysfunction.[19,24] This same mechanism could explain the increased mortality and morbidity burden throughout the first year of life.

Limitations of our study are mostly related to the administrative nature of the dataset. Using ICD-9 codes to identify PPHN and underlying etiology carries a risk of misclassification for those variables. However, this limitation is at least partly offset by the large number of cases identified in this large population-based dataset. We cannot exclude that cases have been missed based on ICD-9 codes used or that inappropriate use of ICD-9 codes for PPHN could have labeled some infants without PPHN as PPHN cases. However, the usage of the ICD-9 codes for PPHN has been validated by a positive predictive value of 68.3%-89.6% when compared with primary medical record review.[25,26] We were also unable to assess timing of the ICD-9 codes. For example, it is possible that the sepsis or infection diagnosis occurred late in the hospital course after diagnosis of PPHN in certain infants, thus, falsely assigning it as the underlying cause. Additionally, we had relatively limited details about the clinical course of the cases with PPHN. For example, it was impossible to confirm the diagnosis of PPHN with echocardiographic data. We were also unable to incorporate potentially important clinical predictors such as oxygen requirement, length of mechanical ventilation, use of inhaled nitric oxide, or extracorporeal membrane oxygenation into our analysis.

It is not unexpected that infants with severe PPHN, or with etiologies at high risk for permanent pulmonary hypertension such as CDH, have a higher mortality and morbidity burden throughout the first year of life than infants without PPHN. However, it is surprising that infants with mild PPHN and more short-term etiologies such as MAS, infection, or RDS still have a significant mortality and morbidity burden beyond the neonatal period compared with infants without PPHN. This information should inform preventive measures and counseling of parents. ■

Submitted for publication Apr 3, 2019; last revision received Jun 4, 2019; accepted Jun 21, 2019.

Reprint requests: Martina A. Steurer, MD, UCSF Department of Pediatrics, 550 16th St, 5th Floor, San Francisco, CA 94143. E-mail: martina.steurermuller@ucsf.edu

## Data statement

Data sharing statement available at www.jpeds.com.

## References


1. Steinhorn RH. Neonatal pulmonary hypertension. Pediatr Crit Care Med 2010;11:S79-84.
2. Oishi PE, Keller RL. When persistent pulmonary hypertension of the newborn persists*. Pediatr Crit Care Med 2012;13:224-5.
3. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics 2000;105:14-20.
4. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med 2000;342:469-74.
5. Roberts JD, Fineman JR, Morin FC, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med 1997;336:605-10.
6. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997;336:597-604.
7. Konduri GG, Vohr B, Robertson C, Sokol GM, Solimano A, Singer J, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. J Pediatr 2007;150:235-40. 240.e1.
8. Clark RH, Huckaby JL, Kueser TJ, Walker MW, Southgate WM, Perez JA, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension: 1-year follow-up. J Perinatol 2003;23:300-3.
9. Group TNINOS. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the neonatal inhaled nitric oxide study group (NINOS). J Pediatr 2000;136:611-7.
10. Ellington M, O'Reilly D, Allred EN, McCormick MC, Wessel DL, Kourembanas S. Child health status, neurodevelopmental outcome, and parental satisfaction in a randomized, controlled trial of nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics 2001;107:1351-6.
11. Group UCE. The collaborative UK ECMO (Extracorporeal Membrane Oxygenation) trial: follow-up to 1 year of age. Pediatrics 1998;101:E1.
12. Baer RJ, Chambers CD, Jones KL, Shew SB, MacKenzie TC, Shaw GM, et al. Maternal factors associated with the occurrence of gastroschisis. Am J Med Genet A 2015;167:1534-41.
13. Baer RJ, Lyell DJ, Norton ME, Currier RJ, Jelliffe-Pawlowski LL. First trimester pregnancy-associated plasma protein-A and birth weight. Eur J Obstet Gynecol Reprod Biol 2016;198:1-6.
14. Jelliffe-Pawlowski LL, Norton ME, Baer RJ, Santos N, Rutherford GW. Gestational dating by metabolic profile at birth: a California cohort study. Am J Obstet Gynecol 2016;214:511.e1-13.
15. Stey A, Barnert ES, Tseng CH, Keeler E, Needleman J, Leng M, et al. Outcomes and costs of surgical treatments of necrotizing enterocolitis. Pediatrics 2015;135:e1190-7.
16. Gage S, Kan P, Lee HC, Gould JB, Stevenson DK, Shaw GM, et al. Maternal asthma, preterm birth, and risk of bronchopulmonary dysplasia. J Pediatr 2015;167:875-80.e1.
17. Jelliffe-Pawlowski LL, Norton ME, Shaw GM, Baer RJ, Flessel MC, Goldman S, et al. Risk of critical congenital heart defects by nuchal translucency norms. Am J Obstet Gynecol 2015;212:518.e1-10.
18. Crisham Janik MD, Newman TB, Cheng YW, Xing G, Gilbert WM, Wu YW. Maternal diagnosis of obesity and risk of cerebral palsy in the child. J Pediatr 2013;163:1307-12.
19. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. Pediatrics 20161-15.
20. Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: the true mortality of congenital diaphragmatic hernia. Pediatrics 2003;112:532-5.
21. Colvin J, Bower C, Dickinson JE, Sokol J. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. Pediatrics 2005;116:e356-63.
22. Burgos CM, Modée A, Öst E, Frenckner B. Addressing the causes of late mortality in infants with congenital diaphragmatic hernia. J Pediatr Surg 2017;52:526-9.
23. Wynn J, Aspelund G, Zygmunt A, Stolar CJH, Mychaliska G, Butcher J, et al. Developmental outcomes of children with congenital diaphragmatic hernia: a multicenter prospective study. J Pediatr Surg 2013;48:1995-2004.
24. Rozance PJ, Seedorf GJ, Brown A, Roe G, O'Meara MC, Gien J, et al. Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction in vitro in fetal sheep. Am J Physiol Lung Cell Mol Physiol 2011;301:L860-71.
25. Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Patorno E, Gopalakrishnan C, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. JAMA 2015;313:2142-51.
26. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernández-Díaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidem Drug Safe 2014;23:646-55.

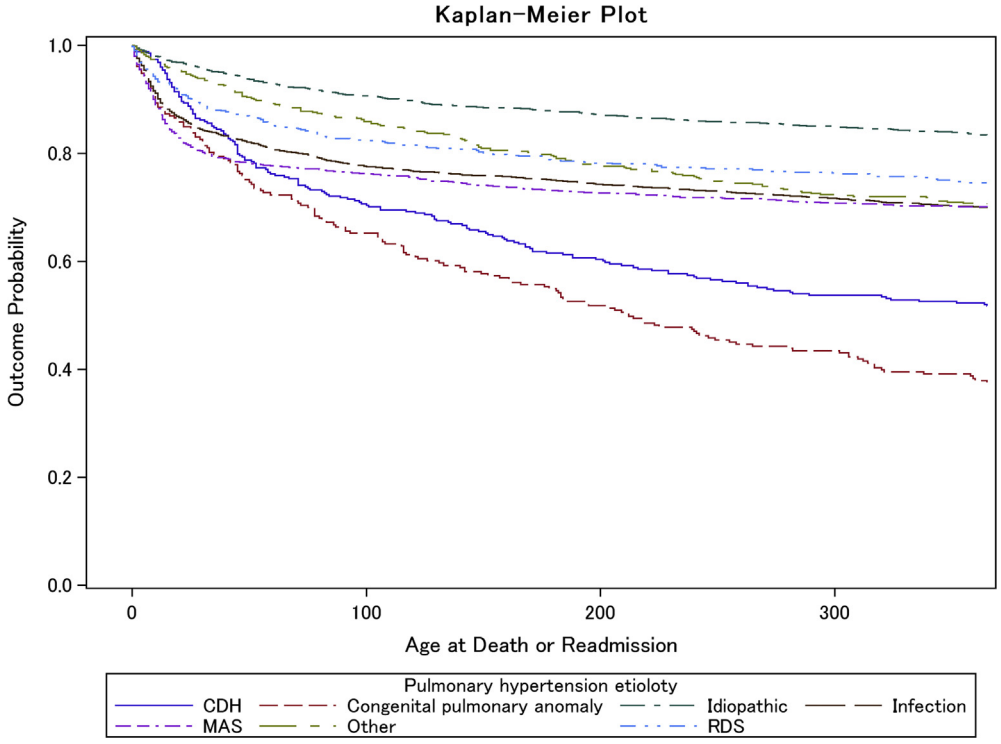


**Figure 2.** Kaplan-Meyer curve for mortality or readmission by PPHN etiology. With no PPHN as the reference group, the following are the HRs and 95% CI associated with the above curves: CDH 6.06 (5.21-7.05), other anomaly of the respiratory system 8.68 (7.43-10.13), MAS 3.61 (3.30-3.96), infection 3.54 (3.29-3.80), RDS 2.83 (2.43-3.31), other 3.24 (2.76-3.80), and idiopathic 1.74 (1.54-1.96).

**Table I. Baseline characteristics of cases and controls**

| Characteristics | All PPHN | Mild PPHN | Severe PPHN | No PPHN | *P* value* |
|---|---|---|---|---|---|
| n | 7847 | 2477 | 5370 | 3 966 689 | |
| Gestational age (weeks) | | | | | |
| <37 | 1423 (18.1) | 304 (12.3) | 1119 (20.8) | 276 243 (7.0) | <.0001 |
| 37-40 | 5567 (70.9) | 1904 (76.9) | 3663 (68.2) | 3 306 715 (83.4) | |
| ≥41 | 857 (10.9) | 269 (10.9) | 588 (11.0) | 383 731 (9.7) | |
| Birth weight | | | | | |
| Small for gestational age | 1056 (13.5) | 258 (10.4) | 798 (14.9) | 372 248 (9.4) | <.0001 |
| Adequate for gestational age | 5383 (68.6) | 1652 (66.7) | 3731 (69.5) | 3 188 112 (80.4) | |
| Large for gestational age | 1408 (17.9) | 567 (22.9) | 841 (15.7) | 406 329 (10.2) | |
| Mode of delivery | | | | | <.0001 |
| Vaginal | 3237 (41.3) | 1215 (49.1) | 2022 (37.7) | 2 700 323 (68.1) | |
| Cesarean | 4610 (58.8) | 1262 (51.0) | 3348 (62.4) | 1 266 366 (31.9) | |
| Race | | | | | <.0001 |
| White not Hispanic | 2325 (29.6) | 750 (30.3) | 1575 (29.3) | 1 062 318 (26.8) | |
| Hispanic | 3326 (42.4) | 1051 (42.4) | 2275 (42.4) | 1 945 596 (49.1) | |
| Black | 705 (9.0) | 209 (8.4) | 496 (9.2) | 208 297 (5.3) | |
| Asian | 890 (11.3) | 285 (11.5) | 605 (11.3) | 484 385 (12.2) | |
| Other | 601 (7.7) | 182 (7.4) | 419 (7.8) | 266 093 (6.7) | |
| Sex | | | | | <.0001 |
| Female | 3256 (41.5) | 1098 (44.3) | 2158 (40.2) | 1 939 602 (48.9) | |
| Male | 4591 (58.5) | 1379 (55.7) | 3212 (59.8) | 2 027 075 (51.1) | |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (0.0) | |
| Gestation | | | | | .3599 |
| Singleton | 7664 (97.6) | 2429 (98.1) | 5235 (97.5) | 3 865 748 (97.5) | |
| Twin | 178 (2.3) | 46 (1.9) | 132 (2.5) | 99 020 (2.5) | |
| Multiple | 5 (0.1) | 2 (0.1) | 3 (0.1) | 1921 (0.1) | |
| Maternal education (years) | | | | | <.0001 |
| <12 | 1932 (24.6) | 618 (25.0) | 1314 (24.5) | 1 020 294 (25.7) | |
| 12 | 2081 (26.5) | 660 (26.7) | 1421 (26.5) | 974 817 (24.6) | |
| >12 | 3513 (44.8) | 1117 (45.1) | 2396 (44.6) | 1 834 515 (46.3) | |
| Missing | 321 (4.1) | 82 (3.3) | 239 (4.5) | 137 063 (3.5) | |
| Payment for delivery | | | | | .0461 |
| Private insurance | 3590 (45.8) | 1136 (45.9) | 2454 (45.7) | 1 871 448 (47.2) | |
| Public insurance | 3830 (48.8) | 1224 (49.4) | 2606 (48.5) | 1 884 634 (47.5) | |
| Self-pay | 149 (1.9) | 43 (1.7) | 106 (2.0) | 79 624 (2.0) | |
| Other | 278 (3.5) | 74 (3.0) | 204 (3.8) | 130 983 (3.3) | |
| Parity | | | | | .0017 |
| Nulliparous | 3214 (41.0) | 998 (40.3) | 2216 (41.3) | 1 555 393 (39.2) | |
| Multiparous | 4633 (59.0) | 1477 (59.6) | 3152 (58.7) | 2 410 750 (60.8) | |
| Maternal age (years) | | | | | <.0001 |
| <18 | 156 (2.0) | 43 (1.7) | 113 (2.1) | 115 004 (2.9) | |
| 18-34 | 5970 (76.1) | 1823 (73.6) | 4147 (77.2) | 3 142 608 (79.2) | |
| >34 | 1721 (21.9) | 611 (24.7) | 1110 (20.7) | 708 888 (17.9) | |
| Maternal BMI | | | | | <.0001 |
| Underweight | 165 (2.1) | 49 (2.0) | 116 (2.6) | 111 646 (2.8) | |
| Normal weight | 2190 (27.9) | 705 (28.5) | 1485 (27.7) | 1 351 199 (34.2) | |
| Overweight | 1382 (17.6) | 470 (19.0) | 912 (17.0) | 705 877 (17.8) | |
| Obese | 1538 (19.6) | 506 (20.4) | 1032 (19.2) | 562 462 (14.2) | |
| Missing | 2572 (30.9) | 747 (30.2) | 1825 (34.0) | 1 225 505 (32.8) | |
| Maternal diabetes | | | | | <.0001 |
| None | 6615 (84.3) | 2040 (82.4) | 4575 (85.2) | 3 619 136 (91.2) | |
| Preexisting | 235 (3.0) | 88 (3.6) | 147 (2.7) | 32 714 (0.8) | |
| Gestational | 997 (12.7) | 349 (14.1) | 648 (12.1) | 314 839 (7.9) | |
| Mental illness | 456 (5.8) | 128 (5.2) | 328 (6.1) | 121 695 (3.1) | <.0001 |
| Smoking during pregnancy | 439 (5.6) | 125 (5.1) | 314 (5.9) | 134 219 (3.4) | <.0001 |
| Illicit drug use | 261 (3.3) | 72 (2.9) | 189 (3.5) | 62 252 (1.6) | <.0001 |
| Maternal asthma | 445 (5.7) | 123 (5.0) | 322 (6.0) | 148 057 (3.7) | <.0001 |
| Hypertension | | | | | <.0001 |
| None | 6929 (88.3) | 2195 (88.6) | 4734 (88.2) | 3 690 836 (93.1) | |
| Preexisting | 223 (2.8) | 72 (2.9) | 151 (2.8) | 54 039 (1.4) | |
| Gestational | 606 (7.7) | 182 (7.4) | 424 (7.9) | 203 327 (5.1) | |
| Unspecified | 89 (1.1) | 28 (1.1) | 61 (1.1) | 18 487 (0.4) | |
| Preeclampsia | 470 (6.0) | 139 (5.6) | 331 (6.2) | 131 518 (3.3) | <.0001 |
| Ventilation | | | | | <.0001 |
| Positive pressure | 4830 (61.6) | 0 (0.0) | 4830 (89.9) | 41 591 (1.1) | |
| CPAP | 540 (6.9) | 0 (0.0) | 540 (10.1) | 34 073 (0.9) | |
| Neither | 2477 (31.6) | 2477 (100.0) | 0 (0.0) | 3 891 025 (98.1) | |
| Days to discharge home (mean, SD) | 23 (35.7) | 14.1 (29.0) | 27.6 (38.0) | 2.8 (7.9) | <.0001 |

*BMI*, body mass index; *CPAP*, continuous positive airway pressure.
Values are number (%) unless otherwise indicated.
**P* value refers to all PPHN vs controls.

**Table III. Mortality, readmissions, or ED visits in first year of life in cases with severe PPHN* vs controls**

| Characteristics | Severe PPHN, n (%) | No PPHN, n (%) | Crude RR (95% CI) | aRR† (95% CI) |
|---|---|---|---|---|
| Entire sample | 5370 | 3 966 689 | | |
| Mortality | | | | |
| No | 4826 (89.9) | 3 960 260 (99.8) | Reference | Reference |
| Yes | 544 (10.1) | 6429 (0.2) | 64.1 (58.7-70.0) | 53.6 (48.9-58.7) |
| Predischarge mortality | 494 (9.2) | 2366 (0.1) | 141.9 (129.4-155.7) | 112.2 (101.7-123.8) |
| Postdischarge mortality | 50 (0.9) | 4063 (0.1) | 10.0 (7.6-13.2) | 8.9 (6.8-11.8) |
| Sample who survived to discharge | 4876 | 3 964 323 | | |
| Readmission | | | | |
| None | 3272 (67.1) | 3 574 165 (90.2) | Reference | Reference |
| Any | 1604 (32.9) | 390 158 (9.8) | 4.5 (4.2-4.8) | 4.2 (3.9-4.4) |
| >1 readmission | 321 (6.6) | 46 190 (1.2) | 7.5 (6.7-8.5) | 6.7 (6.0-7.6) |
| Readmission for respiratory cause | | | | |
| None | 4281 (87.8) | 3 827 826 (96.6) | Reference | Reference |
| Any | 595 (12.2) | 136 497 (3.4) | 3.9 (3.6-4.2) | 3.6 (3.3-4.0) |
| >1 readmission for respiratory cause | 119 (2.4) | 11 971 (0.3) | 8.8 (7.3-10.6) | 7.9 (6.6-9.5) |
| ED visits | | | | |
| None | 3123 (64.1) | 2 589 817 (65.3) | Reference | Reference |
| Any | 1753 (36.0) | 1 374 506 (34.7) | 1.1 (1.0-1.1) | 1.0 (1.0-1.1) |
| >1 ED visit | 846 (17.3) | 595 024 (15.0) | 1.2 (1.1-1.3) | 1.1 (1.1-1.2) |
| ED visits for respiratory cause | | | | |
| None | 3903 (80.1) | 3 289 313 (83.0) | Reference | Reference |
| Any | 973 (20.0) | 675 010 (17.0) | 1.2 (1.1-1.3) | 1.2 (1.1-1.3) |
| >1 ED visit for respiratory cause | 321 (6.6) | 186 850 (4.7) | 1.4 (1.3-1.6) | 1.4 (1.2-1.5) |
| Postdischarge mortality or hospital readmission | | | | |
| No | 3249 (66.6) | 3 571 569 (90.1) | Reference | Reference |
| Yes | 1627 (33.4) | 392 754 (9.9) | 4.5 (4.3-4.8) | 4.2 (4.0-4.5) |

*Severe PPHN is defined as infants receiving positive pressure ventilation or CPAP.
†Adjusted for gestational age, sex, fetal growth, and race/ethnicity.

**Table IV. Mortality, readmissions, or ED visits in first year of life in cases with mild PPHN* vs controls**

| Characteristics | Mild PPHN, n (%) | No PPHN, n (%) | Crude RR (95% CI) | aRR† (95% CI) |
|---|---|---|---|---|
| Entire sample | 2477 | 3 966 689 | | |
| Mortality | | | | |
| No | 2450 (98.9) | 3 960 260 (99.8) | Reference | Reference |
| Yes | 27 (1.1) | 6429 (0.2) | 6.8 (4.6-9.9) | 6.9 (4.7-10.0) |
| Predischarge mortality | 19 (0.8) | 2366 (0.1) | 12.9 (8.2-20.2) | 13.1 (8.3-20.6) |
| Postdischarge mortality | 8 (0.3) | 4063 (0.1) | 3.2 (1.6-6.4) | 3.2 (1.6-6.5) |
| Sample who survived to discharge | 2458 | 3 964 241 | | |
| Readmission | | | | |
| None | 1966 (80.0) | 3 574 165 (90.2) | Reference | Reference |
| Any | 492 (20.0) | 390 158 (9.8) | 2.3 (2.1-2.5) | 2.2 (2.0-2.5) |
| >1 readmission | 105 (4.3) | 46 190 (1.2) | 4.1 (3.4-5.0) | 4.0 (3.3-4.8) |
| Readmission for respiratory cause | | | | |
| None | 2287 (93.0) | 3 827 826 (96.6) | Reference | Reference |
| Any | 171 (7.0) | 136 497 (3.4) | 2.1 (1.8-2.4) | 2.0 (1.7-2.4) |
| >1 readmission for respiratory cause | 32 (1.3) | 11 971 (0.3) | 4.5 (3.1-6.3) | 4.3 (3.0-6.1) |
| ED visits | | | | |
| None | 1565 (63.7) | 2 589 817 (65.3) | Reference | Reference |
| Any | 893 (36.3) | 1 374 506 (34.7) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| >1 ED visit | 402 (16.4) | 595 024 (15.0) | 1.1 (1.0-1.2)‡ | 1.1 (1.0-1.2) |
| ED visits for respiratory cause | | | | |
| None | 2037 (82.9) | 3 289 313 (83.0) | Reference | Reference |
| Any | 421 (17.1) | 675 010 (17.0) | 1.0 (0.9-1.1) | 1.0 (0.9-1.1) |
| >1 ED visit for respiratory cause | 137 (5.6) | 186 850 (4.7) | 1.2 (1.0-1.4) | 1.2 (1.0-1.4) |
| Postdischarge mortality or hospital readmission | | | | |
| No | 1961 (79.8) | 3 571 569 (90.1) | Reference | Reference |
| Yes | 497 (20.2) | 392 754 (9.9) | 2.3 (2.1-2.5) | 2.2 (2.0-2.5) |

*Mild PPHN defined as infants receiving neither positive pressure ventilation nor CPAP.
†Adjusted for gestational age, sex, fetal growth, and race/ethnicity.

**Table V. Incidence, mortality, and readmission for infants with PPHN by year**

| Variables | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | *P* value* |
|---|---|---|---|---|---|---|---|---|---|
| All infants in OSHPD dataset, n | 490 926 | 505 380 | 533 176 | 520 776 | 496 860 | 481 237 | 473 671 | 472 500 | |
| Infants with PPHN, n | 968 | 1062 | 1055 | 991 | 930 | 1019 | 918 | 904 | .0451 |
| Incidence of PPHN, % | 0.20 | 0.21 | 0.20 | 0.19 | 0.19 | 0.21 | 0.19 | 0.19 | |
| Mortality of PPHN, % | 77 (8.0) | 68 (6.4) | 84 (8.0) | 70 (7.1) | 73 (7.9) | 76 (7.5) | 70 (7.6) | 53 (5.9) | .5389 |
| Postdischarge mortality of PPHN, % | 10 (1.0) | 9 (0.9) | 13 (1.2) | 6 (0.6) | 5 (0.5) | 8 (0.8) | 4 (0.4) | 3 (0.3) | .2683 |
| Sample of infants who survived to discharge, n | 901 | 1003 | 984 | 927 | 862 | 951 | 852 | 854 | |
| Readmission | | | | | | | | | |
| Any, % | 284 (31.5) | 292 (29.1) | 331 (33.6) | 277 (29.9) | 233 (27.0) | 246 (25.9) | 225 (26.4) | 208 (24.4) | <.0001 |
| >1 readmission, % | 53 (5.9) | 51 (5.1) | 62 (6.3) | 63 (6.8) | 42 (4.9) | 53 (5.6) | 57 (6.7) | 45 (5.3) | .5167 |
| Readmission for respiratory cause | | | | | | | | | |
| Any, % | 99 (11.0) | 105 (10.5) | 127 (12.9) | 105 (11.2) | 77 (8.9) | 91 (9.6) | 83 (9.7) | 80 (9.4) | .1127 |
| >1 readmission for respiratory cause, % | 12 (1.3) | 16 (1.6) | 18 (1.8) | 24 (2.6) | 12 (1.4) | 19 (2.0) | 25 (2.9) | 25 (2.9) | .0645 |
| Postdischarge mortality or hospital readmission, % | 290 (32.2) | 298 (29.7) | 338 (34.4) | 279 (30.1) | 235 (27.3) | 250 (26.3) | 226 (26.5) | 208 (24.4) | <.0001 |

*$\chi^2$ test.

**Table VIII. Mortality, readmissions, or ED visits in first year of life in cases and controls without chromosomal anomalies or any congenital heart disease**

| Variables | PPHN, n (%) | No PPHN, n (%) | Crude RR (95% CI) | aRR* (95% CI) |
|---|---|---|---|---|
| Entire sample | 5198 | 3 931 139 | | |
| Mortality | | | | |
| No | 4822 (93.0) | 3 925 311 (99.9) | Reference | Reference |
| Yes | 365 (7.0) | 5828 (0.2) | 47.9 (43.1-53.3) | 44.3 (39.8-49.4) |
| Predischarge mortality | 326 (6.3) | 2046 (0.1) | 111.8 (99.9-125.0) | 101.7 (90.5-114.3) |
| Postdischarge mortality | 39 (0.8) | 3782 (0.1) | 8.3 (6.1-11.4) | 7.9 (5.8-10.9) |
| Sample who survived to discharge | 4872 | 3 929 093 | | |
| Readmission | | | | |
| None | 3670 (75.3) | 3 551 821 (90.4) | Reference | Reference |
| Any | 1202 (24.7) | 377 272 (9.6) | 3.1 (2.9-3.3) | 2.9 (2.7-3.1) |
| >1 readmission | 195 (4.0) | 42 620 (1.1) | 4.4 (3.8-5.1) | 4.1 (3.5-4.7) |
| Readmission for respiratory cause | | | | |
| None | 4462 (91.6) | 3 797 938 (96.7) | Reference | Reference |
| Any | 410 (8.4) | 131 155 (3.3) | 2.7 (2.4-2.9) | 2.5 (2.3-2.8) |
| >1 readmission for respiratory cause | 71 (1.5) | 10 889 (0.3) | 5.5 (4.4-7.0) | 5.1 (4.0-6.5) |
| ED visits | | | | |
| None | 3149 (64.6) | 2 569 669 (65.4) | Reference | Reference |
| Any | 1723 (35.4) | 1 359 424 (34.6) | 1.0 (1.0-1.1) | 1.0 (1.0-1.1) |
| >1 ED visit | 812 (16.7) | 587 533 (15.0) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| ED visits for respiratory cause | | | | |
| None | 3979 (81.7) | 3 261 961 (83.0) | Reference | Reference |
| Any | 893 (18.3) | 667 132 (17.0) | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) |
| >1 ED visit for respiratory cause | 301 (6.2) | 184 320 (4.7) | 1.3 (1.2-1.5) | 1.3 (1.1-1.5) |
| Postdischarge mortality or hospital readmission | | | | |
| No | 3649 (74.9) | 3 549 325 (90.3) | Reference | Reference |
| Yes | 1223 (25.1) | 379 768 (9.7) | 3.1 (2.9-3.3) | 3.0 (2.8-3.2) |

ICD-9 codes for chromosomal anomalies are 759.0-759.9.
*Adjusted for gestational age, sex, fetal growth and race/ethnicity.