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Morbidity and mortality with early pulmonary haemorrhage in preterm neonates

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ABSTRACT

Objective There are no large studies evaluating pulmonary haemorrhage (PH) in premature infants. We sought to quantify the clinical characteristics, morbidities and mortality associated with early PH.

Design Data were abstracted from the Pediatrix Clinical Data Warehouse, a large de-identified data set. For incidence calculations, we included infants from 340 Pediatrix United States Neonatal Intensive Care Units from 2005 to 2014 without congenital anomalies. Infants <28 weeks' gestation with PH within 7 days of birth were then matched with two controls for birth weight, gestational age, gender, antenatal steroid exposure, day of life 0 or 1 intubation and multiple gestation.

Results From 596 411 total infants, we identified 2799 with a diagnosis of PH. Peak incidence was 86.9 cases per 1000 admissions for neonates born at 24 weeks' gestation. We then identified 1476 infants <28 weeks' gestation with an early PH diagnosis at ≤7 days of age of which 1363 (92.3%) were successfully matched. Patients with early PH had significantly higher exposure to poractant alfa (35.4% vs 28%), diagnosis of shock (63.7% vs 51%) and grade IV intraventricular haemorrhage (20.8% vs 6%). Patients with PH also had significantly higher mortality rates at 7 days of age (40.6% vs 18.9%), 30 days of age (54% vs 28.8%) and prior to discharge (56.9% vs 33.7).

Conclusion In this large cohort of premature infants, we found PH to be common among the most premature babies. Early PH was associated with significant morbidity and mortality in excess of 50%. A renewed focus on the underlying pathophysiology and prevention of PH is warranted.

What is already known on this topic?

- Pulmonary haemorrhage is a severe complication of preterm birth and can lead to increased morbidity and mortality.
- Pulmonary haemorrhage has an association with patent ductus arteriosus and can be prevented with prophylactic indomethacin.

What this study adds?

- In a large cohort, pulmonary haemorrhage is most common among 23 and 24 weeks' gestation infants with 86 and 86.9 cases per 1000 patients.
- At <28 weeks' gestation, pulmonary haemorrhage cases occur most commonly on the first (24%) and second (33%) days after birth.
- Early pulmonary haemorrhage among infants <28 weeks' gestation is associated with an increased mortality at 7 days (40.6% vs 18.9%) and overall (56.9% vs 33.7%).

BACKGROUND

Contemporary incidence and clinical sequelae of neonates with pulmonary haemorrhage (PH) have not been well described in the literature. Prior investigations of PH have come from single-centre studies with small number of patients[1–4] or from a secondary analysis of older trials that occurred prior to the widespread use of surfactant and antenatal steroids, with limited generalisability to current infants.[5] These reports suggest that infants with PH have an increased risk of death in addition to other potentially catastrophic effects.[1 4 6] Despite this, there have been no large descriptions of the demographics, morbidity and mortality of patients diagnosed with neonatal PH in a contemporary population. Our objective was to describe a population of premature infants with early pulmonary haemorrhage (EPH) within the first 7 days after birth and to quantify the association between EPH, major morbidities and mortality in a large multicentre cohort in the USA. We hypothesised that early neonatal pulmonary haemorrhage would be associated with significantly excess hospital morbidity and mortality.

METHODS

Study design

We performed a retrospective cohort study of infants from the Pediatrix Medical Group Clinical Data Warehouse (CDW), a large, multicenter, de-identified data set.

Study population

Our cohort initially included all inborn infants from 340 Pediatrix-managed neonatal intensive care units (NICUs) within the USA who were cared for from day of life 0 or 1 through death or discharge between 1 January 2005 and 31 December 2014. We excluded infants with significant congenital anomalies. This population was utilised to calculate incidence data. We then restricted our analysis to just those infants <28 weeks' gestation at birth to calculate

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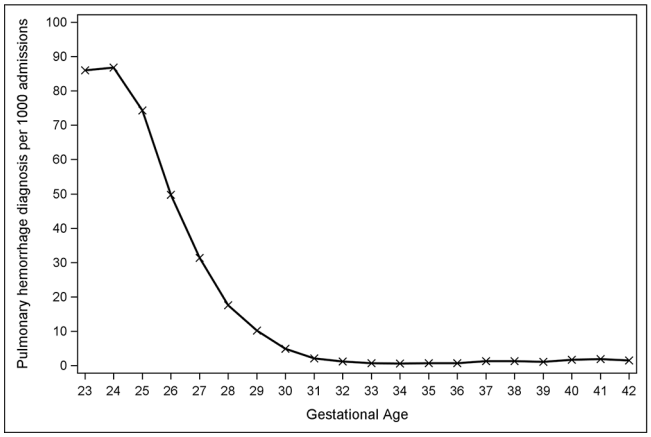

Figure 1 Incidence of pulmonary haemorrhage by gestational age. Among pulmonary haemorrhage cases without congenital anomalies and admitted to a Pediatrix Neonatal Intensive Care Unit from day 0 or 1 of life through death or discharge, the incidence of pulmonary haemorrhage is highest for the most preterm neonates. This gradually falls through 32 weeks' gestation after which a baseline rate is maintained.

age distribution for onset of PH. Lastly, we restricted our cohort to those infants both <28 weeks' gestation at birth and with onset of PH within 7 days of birth to isolate those premature infants with early onset PH. We then utilised this cohort for matching 1:2 with control patients.

Data set

Data sourced from the CDW are generated from Babysteps, a standardised documentation and billing software tool used by participating NICUs managed by Pediatrix Medical Group. The CDW captures data prospectively until discharge or death. Local data are consolidated within the CDW, de-identified and made compliant with Health Insurance Portability and Accountability Act of 1996 regulations.

Data analysis

For this analysis, we queried the following specific CDW tables: demographics, diagnoses, procedures and medications. We defined infants with PH as those who were assigned a diagnosis of 'pulmonary haemorrhage' (International Classification of Disease Revision 9 code 770.3) by a clinician. Each PH diagnosis has a date of onset as coded by the clinician.

Our primary interest was EPH in extremely premature infants, so we also created a matched sample of infants less than 28 weeks' gestation at birth with PH within the first 7 days of life and matched these infants in a 1:2 ratio of cases to controls for further detailed analysis. Matching variables included gestational age, birth weight, gender, intubation on day of life 0 or 1, antenatal steroid exposure and multiple gestation. Comparisons between the case and control groups were performed using t-tests for numerical variables and X^2 tests for categorical variables. The same analysis was also used to compare EPH survivors and decedents. All analyses were performed using SAS V.9.4 with a significance level of 0.05.

RESULTS

Between 2005 and 2014, we identified a total 596 411 infants cared for in a Pediatrix-associated NICU from day of life 0 or 1 through death or discharge, excluding those with major congenital anomalies. Of these, 2799 had a PH diagnosis. We found the highest incidence of PH to be among neonates born at 23 and 24 weeks' gestation, with a PH incidence of 86 and 86.9 cases per 1000 admissions, respectively, and a gradual decline at higher gestations (figure 1). The incidence of PH for infants ≥32 weeks' gestation ranged from 0.6 to 1.9 cases per 1000 admissions.

Among infants less than 28 weeks' gestation at birth, PH diagnosis was most common on the first (24%) and second (33%) days after birth with a rapid decline thereafter through the first week. Pulmonary haemorrhage occurred beyond the first week after birth in 19% of cases. Based on the gestational age and timing after birth distributions of PH, we chose to further examine patients <28 weeks' gestation with early pulmonary haemorrhage within 7 days of birth in a matched sample, leaving 1476 infants available for matching. Successful case–control matching was possible for 1363 of the 1476 eligible infants (92.3%).

In the matched sample, infants with EPH were more likely to be born via vaginal delivery (26.6% vs 20.8%, P<0.0001), but had no differences in delivery room intubation rates, cardiopulmonary resuscitation (CPR) or 1 and 5 min Apgar scores compared with controls (table 1). Among surfactants, only poractant alfa had a significantly higher percentage of use among EPH cases versus controls (35.4% vs 28%, P<0.0001).

An evaluation of outcomes in the matched sample (table 2) finds that infants with EPH had significantly higher rates of respiratory distress syndrome, pneumothorax, patent ductus arteriosus (PDA), shock and severe (grades III and IV) intraventricular haemorrhage (IVH) compared with controls. These patients also had significantly higher mortality rates compared with matched controls at 7 days of age (40.6% vs 18.9%, P<0.0001), 30 days of age (54% vs 28.8%, P<0.0001) and prior to discharge (56.9% vs 33.7, P<0.0001). Mortality for these cases is visualised with a Kaplan-Meier survival plot (figure 2).

We also compared EPH survivors with decedents (table 3). Survivors had more frequent exposure to antenatal steroids, more likely to be born via caesarean delivery and had significantly higher gestational age and birth weight. Survivors also had significantly lower exposure to pressors. Early pulmonary haemorrhage survivors had significantly less shock and grade IV IVH but more PDA and necrotising enterocolitis.

DISCUSSION

In this contemporary, large, multicentre cohort of premature infants, we found EPH to be a common complication of extreme prematurity. The size of our overall cohort allowed us to generate the first gestational week-specific incidence data for this condition and first survival curves that demonstrate the timing of mortality of these patients in comparison to a matched control group. We found the incidence of EPH to rise with increasing prematurity. The incidence of almost 9% at 23 weeks and 24 weeks is comparable to that of surgical necrotising enterocolitis.[7] With an associated mortality of 40.6% within the first week after birth and 56.9% overall, the diagnosis of EPH strongly correlates with overall mortality in this cohort. We found this mortality rate to be significantly higher than for controls even after matching for known mortality risk factors. Our baseline mortality rate is similar to Ferreira *et al*'s, Chen *et al*'s and Scholl and Yanowitz's [1 2 4] or prior reports and higher than Alfaleh *et al*'s.[6]

Table 1 Demographic characteristics and medication exposures in the matched sample

	Diagnosis of PH	No diagnosis of PH	
	n = 1363	n=2726	P value
Maternal characteristics			
Age	26.8±6.5	27.3±6.4	0.8897
Multiple gestation (%)*	429 (31.5)	858 (31.5)	1.0
Antenatal steroids exposure (%)*	864 (63.4)	1728 (63.4)	1.0
Maternal chorioamnionitis (%)	58 (4.3)	185 (6.8)	0.0012
Infant characteristics			
Gestational age (mean±SD)*	24.9±1.3	24.9±1.3	1.0
Birth weight (mean±SD)*	722.2±186.3	723.1±229.1	0.8897
Female gender (%)*	561 (41.2)	1122 (41.2)	1.0
Infant medication exposure			
All indomethacin exposure (%)	470 (34.5)	996 (36.5)	0.1966
Early indomethacin exposure, day 0 or 1 of hospital stay (%)	197 (14.5)	465 (17.1)	0.0331
Surfactant exposure (%)**	1224 (89.8)	2307 (84.6)	<0.0001
Beractant (%)	470 (34.5)	880 (32.3)	0.0646
Poractant alfa (%)	482 (35.4)	763 (28)	<0.0001
Calfactant	301 (22.1)	687 (25.2)	0.0281
Brand not specified	9 (0.7)	19 (0.7)	0.8933
Hydrocortisone (%)	482 (35.4)	798 (29.3)	<0.0001
Dexamethasone (%)	214 (15.7)	546 (20)	0.0008
Diuretics (furosemide, spironolactone or chlorothiazide) (%)	592 (43.4)	1445 (53)	<0.0001
Inhaled fluticasone or beclomethasone (%)	100 (7.3)	224 (8.2)	0.3258
Albuterol (%)	283 (20.8)	708 (26)	0.0002
Nitric oxide (%)	101 (7.4)	208 (7.6)	0.8018
Dopamine (%)	904 (66.3)	1385 (50.8)	<0.0001
Dobutamine (%)	327 (24)	467 (17.1)	<0.0001
Epinephrine (%)	318 (23.3)	386 (14.2)	<0.0001

*Matching variable.
**Some infants received two types of surfactant resulting in the total number of surfactant exposed patients to be less than individual types.

The diagnosis of pulmonary haemorrhage has been strongly correlated with the presence of a haemodynamically significant PDA.[8 9] The significant PDA results in large volume ductal shunting,[10] excessive pulmonary blood flow[9] and haemorrhagic pulmonary oedema.[11] Early PDA screening,[12] early PDA therapy[13] and indomethacin prophylaxis[6] have all been found to reduce the incidence of pulmonary haemorrhage in very preterm infants but not overall survival. However, interpretation of clinical trials in this area has often been complicated by open-label rescue therapy available to the placebo groups.[13 14]

Our findings are consistent with these earlier reports. We found a significantly lower exposure to early indomethacin (day 0 or 1 after birth) among EPH cases compared with controls. We also found a significantly higher incidence of both PDA diagnosis and PDA ligation among EPH cases compared with matched controls. In examining EPH survivors, the PDA diagnosis and ligation rates rise further to 72.6% and 11.2%, respectively, compared with 43.5% and 4.9% among the non-EPH control group. This finding may be attributable to survivorship bias as we also note in the higher rates of bacteraemia and necrotising enterocolitis among EPH survivors compared with either the EPH decedent group or the non-EPH matched control group.

The use of surfactant products in very preterm infants has been correlated with pulmonary haemorrhage.[5] Surfactant use in this population is associated with a fall in pulmonary vascular resistance that leads to decreased pulmonary artery pressures and increased blood flow across the PDA.[15] In this cohort, patients with EPH had significantly higher overall exposures to surfactant products, largely driven by a significantly higher rate of poractant alfa exposure, compared with matched controls. Early trials of poractant alfa did not find a similar association;[16–18] however, these trials enrolled few of the 23 and 24 weeks' infants most likely to experience PH. A more recent trial[19] enrolled more extremely preterm infants but as with the early trials likely did not have sufficient power to detect such an association.

Although our study is limited to associations, we believe that EPH plays an important role in mortality in part because most EPH occurred shortly after birth and the differences in mortality rates in the match sample were highest for early mortality. However, the mechanism by which EPH contributes to the mortality of preterm infants remains outside the scope of this report. Early PH may play a central role in the causal pathway of mortality, or it be part of a multifactorial decision regarding withdrawal of care including the described co-occurrences of severe IVH, shock and need for high frequency ventilation.

Little is known about factors that are associated with survival in patients with EPH. In our cohort, survivors had a greater gestational age and a birth weight 100 g greater than decedents. Survivors of EPH had a significantly higher antenatal steroid exposure and caesarean section rates as well as lower need for CPR in the delivery room. Early PH decedents had significantly higher exposures to dopamine, dobutamine and epinephrine compared with EPH survivors. We did not find a difference in grade III IVH among these groups, but found that 27% of non-survivors had a diagnosis of grade IV IVH. It is possible that

Table 2 Patient outcomes in the matched sample

	Pulmonary haemorrhage n=1363	No pulmonary haemorrhage n=2726	P value
Respiratory features			
Respiratory distress syndrome diagnosis (%)	1309 (96)	2550 (93.5)	0.0011
Age at initial extubation (days±SD)	9.5±14.2	9.9±14.8	0.5545
Pneumothorax (%)	133 (9.8)	206 (7.6)	0.0161
Associated diagnoses			
Intraventricular Haemorrhage (maximum grade)			
Grade I (%)	131 (9.6)	312 (11.4)	< 0.0001
Grade II (%)	116 (8.5)	218 (8)	
Grade III (%)	149 (10.9)	150 (5.5)	
Grade IV (%)	283 (20.8)	164 (6)	
Periventricular leukomalacia (%)	48 (3.5)	75 (2.8)	0.1740
Diagnosis of 'shock' or 'hypotension' (%)	868 (63.7)	1389 (51)	<0.0001
Patent ductus arteriosus (%)	707 (51.9)	1185 (43.5)	<0.0001
Patent ductus arteriosus ligation (%)	85 (6.2)	133 (4.9)	0.0686
Positive blood culture (%)	279 (20.5)	760 (27.9)	<0.0001
Any necrotising enterocolitis (suspected, medical, surgical) (%)	121 (8.9)	344 (12.6)	0.0004
Outcomes			
Pulmonary disposition at 36 weeks			
Dead (%)	767 (56.3)	889 (32.6)	< 0.0001
Severe BPD—nasal cannula >2 LPM or any positive pressure at 36/0 weeks (%)	196 (14.4)	565 (20.7)	
In NICU on mild respiratory support (<2 LPM nasal cannula) (%)	207 (15.2)	459 (16.8)	
In NICU without respiratory support (%)	98 (7.2)	410 (15.0)	
Discharged home with support (%)	71 (5.2)	200 (7.3)	
Discharged home without support (%)	24 (1.8)	203 (7.4)	
Length of stay, median (IQR), days			
All	12 (2, 91)	74 (10, 101)	<0.0001
Died	3 (2, 7)	4 (1, 16)	0.2615
Survived	95 (78, 112)	91 (73, 113)	0.0548
Mortality			
7 days (%)	553 (40.6)	516 (18.9)	<0.0001
30 days (%)	736 (54)	784 (28.8)	<0.0001
Prior to discharge (%)	775 (56.9)	919 (33.7)	<0.0001

BPD, bronchopulmonary dysplasia; LPM, litres per minute; NICU, neonatal intensive care unit.

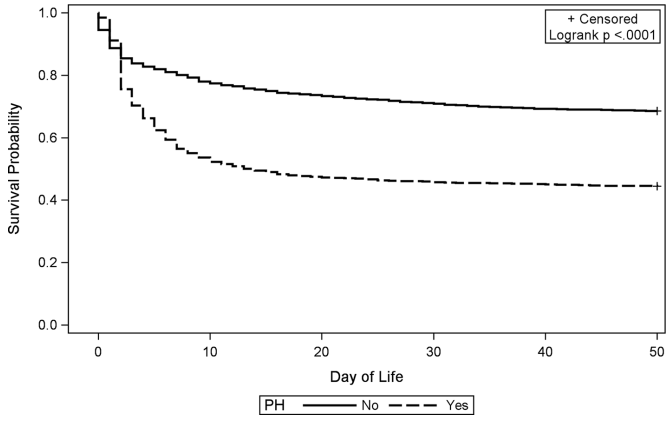

Figure 2 Kaplan-Meier plot of survival through the first 50 days of life in the matched sample. A survival plot comparing patients less than 28 weeks' gestation with early pulmonary haemorrhage with matched controls. Patients with early pulmonary haemorrhage (PH) have significant excess mortality which is most prominent through the first 10 days after birth.

we have underestimated the rate of grade IV IVH in decedents as they may have expired prior to completing a head ultrasound. Without data regarding severity of individual PH diagnoses, it is challenging to draw conclusions regarding how these findings associate directly with survival in this cohort.

The major strengths of our study are the large number and diversity of NICUs that contribute to this database as well as the large number of patients with pulmonary haemorrhage over 10 years. We obtained a robust 1:2 match across six variables for 92.3% of our EPH cases. Our study also has several limitations. In the CDW, a diagnosis of 'pulmonary haemorrhage' is not standardised across the network. Nor does it include any modifier to determine the severity of PH. Thus, our cohort includes a wide range in severity of cases. Further, data collection within the CDW occurs once daily. As a result, the exact relationship of ventilator changes, medication dosing and onset of PH within the same day is unavailable, and thus we are unable to describe the temporal relation of PH to other factors.

In conclusion, we provide the first gestational age-specific incidence curves and survival curves for very preterm infants diagnosed with early pulmonary haemorrhage. We are not

Table 3 Comparison of early pulmonary haemorrhage survivors and decedents

	Survivors	Decedents	
	n=588	n=775	P values
Maternal characteristics			
Antenatal steroids exposure (%)	409 (69.6)	455 (58.7)	<0.0001
Maternal chorioamnionitis (%)	26 (4.4)	32 (4.1)	0.7909
Infant characteristics			
Gestational age (mean±SD)	25.4±1.2	24.6±1.3	<0.0001
Female gender (%)	251 (42.7)	310 (40)	0.3181
Birth weight	778.5±181.2	679.5±178.8	<0.0001
Delivery room information			
Delivery method—vaginal (%)	94 (16)	189 (24.4)	0.0002
Delivery room intubation (%)	463 (78.7)	582 (75.1)	0.1151
Delivery room cardiopulmonary resuscitation (%)	10 (1.7)	40 (5.2)	0.0008
Apgar score			
1 min (IQR)	4 (3, 6)	3 (2, 5)	<0.0001
5 min (IQR)	7 (6, 8)	6 (5, 8)	<0.0001
5 min Apgar score <5	90 (15.3)	200 (25.8)	<0.0001
Medication exposure			
Nitric oxide (%)	45 (7.7)	56 (7.2)	0.7655
Dopamine (%)	335 (57)	569 (73.4)	<0.0001
Dobutamine (%)	82 (13.9)	245 (31.6)	<0.0001
Epinephrine (%)	50 (8.5)	268 (34.6)	<0.0001
Associated diagnoses			
Intraventricular haemorrhage (maximum grade)			
Grade I (%)	99 (16.8)	32 (4.1)	< 0.0001
Grade II (%)	78 (13.3)	38 (4.9)	
Grade III (%)	66 (11.2)	83 (10.7)	
Grade IV (%)	74 (12.6)	209 (27)	
Diagnosis of 'shock' or 'hypotension' (%)	334 (56.8)	534 (68.9)	<0.0001
Patent ductus arteriosus (%)	427 (72.6)	280 (36.1)	<0.0001
Patent ductus arteriosus ligation (%)	66 (11.2)	19 (2.5)	<0.0001
Positive blood culture (%)	190 (32.3)	89 (11.5)	<0.0001
Any necrotising enterocolitis (suspected, medical, surgical) (%)	79 (13.4)	42 (5.4)	<0.0001

aware of any other common condition in very premature infants associated with over 50% mortality. These data emphasise that EPH is a significant and continuing area of morbidity and mortality in this population. There remains a strong need for further studies that focus on the underlying prevention of EPH, which may yield outsized benefit in improving the survival and outcomes of the most premature patients. These studies likely require further focus on PDA prevention, early detection and early therapy.

Contributors KAA conceptualised and designed the study, analysed and interpreted the data, drafted the initial manuscript and approved the final manuscript as submitted. RHC and VNT conceptualised and designed the study, analysed and interpreted the data, critically reviewed and revised the manuscript and approved the final manuscript as written. MMB carried out the data analyses, critically reviewed and revised the manuscript and approved the final manuscript as written. SFA designed the study, analysed and interpreted the data, critically reviewed and revised the manuscript and approved the final manuscript as written.

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Data sharing statement Data from the Pediatrix Clinical Data Warehouse is not publicly available.

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