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Factors Associated with Newborn Fatality Due to Persistent Pulmonary Hypertension

Kang Zeng [1], A-Juan Huang [1], Yun-Xia Sun [2], Jin Zhong [2], Man-Li Zheng [2], You-Qun Zou [2], Xin Sun [2] and Yu-Mei Liu [1, 2, *]

[1] Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong, China
[2] Department of Neonatology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangdong, China

[*] *Corresponding author*: Department of Neonatology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangdong, China. Email: 13501519292@139.com

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Abstract

Objectives: This study is designed to explore factors associated with death in newborns with persistent pulmonary hypertension (PPHN).
Methods: The clinical data of PPHN cases in the past ten years from a neonatal center in China were retrospectively collected and analyzed, and the death-related factors attributable to PPHN were analyzed by binary stepwise logistic regression analysis.
Results: A total of 161 neonates with PPHN were included in this study, with a mortality rate of 18.0% (29/161). Multivariate binary logistic regression analysis indicated that cesarean delivery was negatively associated with death in infants with PPHN (adjusted odds ratio [OR] = 0.289, 95% confidence interval [CI] 0.104 - 0.803), while premature rupture of membranes (PROM) (adjusted OR = 4.032, 95% CI 1.32 - 12.32), congenital lung developmental abnormalities/congenital diaphragmatic hernia (CDH) (adjusted OR = 12.65, 95% CI 1.088 - 147.068), respiratory distress syndrome (RDS) (adjusted OR = 4.802, 95% CI 1.512 - 15.251), inhaled nitric oxide (iNO) (adjusted OR = 12.377, 95% CI 3.22 - 47.576) and norepinephrine (adjusted OR = 2.891, 95% CI 1.03 - 8.118) were the independent factors associated with a higher risk of death from PPHN.
Conclusions: Caesarean delivery with medical indication is an independent protective factor against death in neonates with PPHN. PROM, congenital lung developmental abnormalities/CDH, RDS, iNO, and norepinephrine were independent death-related factors in neonates with PPHN.

Keywords: Persistent Pulmonary Hypertension, Infant, Newborn, Risk Factors, Vascular Resistance

1. Background

After birth, the fetal circulation transitions to postnatal circulation, with a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow (1, 2). When this process is blocked, the pulmonary vascular resistance continues to rise, resulting in persistent pulmonary hypertension of the newborn (PPHN), which presents with severe cyanosis and refractory hypoxemia (1). It was previously believed that PPHN frequently occurs in term or late-preterm infants, and the incidence rate varied from 0.12% to 0.46% in different areas (3-5). However, a retrospective, multicentre cohort study reported that the prevalence of PPHN among extremely preterm infants was as high as 8.1% (6).

PPHN is a common critical illness found in the neonatal intensive care unit, with a widely varying mortality rate (7.0% - 36.4%) depending upon the level of health care (3-5, 7, 8). Based on a few clinical studies, factors inconsistently suggested to be associated with a higher risk of a poor prognosis (e.g., death) for PPHN included congenital diaphragmatic hernia (CDH), pulmonary hypoplasia, small for gestational age (< 34 weeks), high-frequency ventilation, and pneumothorax (3, 4, 9, 10). Despite the introduction of treatments such as nitric oxide, extracorporeal membrane oxygenation (i.e., heart–lung bypass), and advanced modes of mechanical ventilation, 10% to 20% of the affected infants used to perish due to limited knowledge of factors that predicted which infants were at the highest risk for death from PPHN (7, 8, 11, 12).

2. Objectives

The objective of this study was to identify additional possible related factors for death from PPHN by retrospectively analyzing the data of neonates diagnosed with PPHN in the neonatal intensive care unit of our hospital from 2010 to 2020, thus improving the risk-stratification in clinical decision-making and potentially improve the prognosis for neonates with PPHN.

3. Methods

3.1. Study Design and Population

This was a single-center, retrospective study. Neonates diagnosed with PPHN from January 1, 2010, to December 31, 2020 in the Neonatal Intensive Care Unit (NICU) of Guangdong Provincial People's Hospital were selected. The inclusion criteria for diagnosis of PPHN were as follows: (1) continuous hypoxemia, arterial partial pressure of oxygen (PaO_2) < 50 mmHg, 100% oxygen inhaled by hooded oxygen or continuous positive airway pressure (CPAP) with no improvement in cyanosis for 5 - 10 minutes; (2) under proper ventilation, severe cyanosis and hypoxemia occurred in the early stage of birth, and the chest X-ray lesions were inconsistent with the degree of hypoxia, symptoms, and signs; (3) an ultrasound ECG showed the presence of a right-to-left shunt at the ductus arteriosus and foramen ovale level. The exclusion criteria were cyanotic congenital heart disease and pneumothorax.

Neonates with a cure clinical outcome were assigned to the survival group, and those with death outcomes were assigned to the non-survival group. The clinical characteristics and related variables were collected, including demographics, comorbidities, medications, and treatments. This study was approved by the ethics review committee of Guangdong Provincial People's Hospital with the ethics number KY-Q-2021-226-01. The requirement of informed consent was waived due to the study's retrospective design.

3.2. Definitions

Intrauterine infection was diagnosed by blood test or amniotic fluid test. Transient tachypnoea of the newborn and neonatal amniotic fluid inhalation was identified by symptoms and X-ray imaging. Newborns with hypoxic respiratory failure with PPHN with oxygenation index $\geq$ 16 were treated with iNO. Developmental Congenital abnormalities include pulmonary vascular and parenchymal development abnormalities, which in this study included pulmonary hypoplasia and dysplasia, congenital diaphragmatic hernia and pulmonary vascular malformation. Respiratory distress syndrome (RDS) was defined as a diffuse lung disease caused by a deficiency of pulmonary surfactant, and lung infections, amongst other causes. Advanced maternal age was defined as a maternal age of more than 35 years.

3.3. Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation ($\bar{x}$ ± SD) or median (interquartile range), and the chi-square test was used to compare the two groups. Nominal qualitative data between the groups were expressed as ratios (%) and compared using the chi-square test or Fisher's exact test, as appropriate. A P value of < 0.05 was considered statistically significant. First, a univariate analysis was used to screen the potential factors associated with death in infants with PPHN (P < 0.05). Then, the stepwise logistic regression analysis was performed to exclude the confounding factors in the multivariate model. This statistical method was chosen because it takes into account the fit of the analytical model and makes the results more reliable, despite its partial drawbacks. Adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI) were retrieved from this model. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS Statistics 25.0 software (IBM Corp. Silicon Valley, CA, US).

4. Results

4.1. General Information About Infants with PPHN

A total of 161 infants with PPHN were included in this study, with a mortality rate of 18.0% (29/161). The results of the univariate analysis for the survival and non-survival group are shown in Table 1. The non-survival group comprised a significantly higher proportion of infants with a gestational age < 34 weeks than the survival group (44.8% versus 25.8%, P = 0.041). In contrast, the infants in the survival group were more likely to be delivered by cesarean section compared with the non-survival group (68.2% versus 34.5%, P = 0.001) (Table 1).

4.2. The Primary and Perinatal Diseases in PPHN

In this study, statistics on the common primary and perinatal disorders of PPHN revealed that the incidence of RDS (58.6% versus 35.6%, P = 0.022), sepsis (44.8% versus 16.7%, P < 0.001), congenital lung developmental abnormalities/CDH (10.3% versus 0.8%, P = 0.019), pneumothorax (34.5% versus 10.6%, P = 0.003) and severe intraventricular hemorrhage (27.6% versus 9.8%, P = 0.028) was significantly higher in the non-survival group than in the survival group (Table 1).

4.3. Basic Maternal Characteristics and Diseases During Pregnancy

Infants in the non-survival group had a higher probability of premature rupture of membranes (PROM) than the infants in the survival group (35.7% versus 9.8%, P = 0.001) (Table 1). However, there was no significant difference between the two groups in terms of the maternal age, adverse maternal history, or other pregnancy-related diseases (P > 0.05) (Table 1).

4.4. Treatment

Conventional treatment options for PPHN are presented in Table 1. This study revealed that infants in the non-survival group were statistically more likely to have received inhaled nitric oxide (iNO) (31.0% versus 6.1%, P < 0.001), milrinone (72.4% versus 43.9%, P = 0.005), high-frequency ventilation (72.4% versus 50.8%, P = 0.034) and norepinephrine (48.3% versus 26.5%, P = 0.021) than the infants in the survival group (Table 1).

4.5. Related Factors for Death from PPHN

Multivariate binary logistic regression analysis indicated that cesarean delivery was a protective factor against death in infants with PPHN (adjusted OR = 0.289, 95% CI 0.104 – 0.803) (Table 2). However, PROM (adjusted OR = 4.032, 95% CI 1.32 - 12.32), congenital lung developmental abnormalities/CDH (adjusted OR = 12.65, 95% CI 1.088 – 147.068), RDS (adjusted OR = 4.802, 95% CI 1.512 - 15.251), iNO (adjusted OR = 12.377, 95% CI 3.22 – 47.576) and norepinephrine (adjusted OR = 2.891, 95% CI 1.03 - 8.118) were independent factors associated with an increased mortality due to PPHN (Table 2).

5. Discussion

In this study, we explored the potential factors related to high mortality due to PPHN in newborns in our institution. The main findings were as follows: (1) there was a mortality rate of 18.0% in the 161 included neonates with PPHN; (2) cesarean delivery was negatively associated with death in infants with PPHN while PROM, CDH, RDS, iNO, and norepinephrine were positively determinants. The present study's findings indicate that these related factors should be considered in clinical decision-making, and the appropriate intervention should be considered as early as possible.

5.1. Caesarean Delivery

This study indicated that cesarean delivery was associated with a decreased risk of death from PPHN; however, it has been recognized as a determinant for developing PPHN, as reported in previous studies (13-15). Some studies observed that cesarean delivery reduced the adverse effects of intrauterine growth restriction, maternal gestational hypertension, and placental dysfunction in newborns (15) and reported that cesarean delivery reduced the risk of neonatal sepsis, intrapartum asphyxia, and intracranial haemorrhage (16). Berhan and Haileamlak (17) and Villar et al. (18) reported that the risk of postnatal asphyxia and fetal faecal aspiration was lower in foetuses delivered by cesarean section in abnormal fetal positions, such as breech previa. Therefore, we believe that cesarean delivery can mitigate the effects of adverse factors (such as asphyxia, meconium aspiration, and sepsis) on the progress of PPHN, which can reduce the mortality rate. Furthermore, we performed a statistical analysis on the reasons for cesarean delivery and found that 93% (93/100) of the cases met the indications of a medical cesarean delivery (Table 3) (19), which supported our perspectives. Thus, 'guideline-compliant' cesarean delivery may be beneficial in modifying the factors related to high mortality in infants with PPHN.

5.2. Premature Rupture of Membranes

We found that newborns presenting with PPHN after premature rupture of membranes had a significantly higher risk for death. Several studies reported that PROM was a predictor for PPHN development, but its impact on the PPHN prognosis is unclear (6, 20, 21). Our findings refined the effect of PROM on PPHN. It may be because PROM can lead to decreased amniotic fluid, fetal inflammatory syndrome, and triggering of preterm delivery, which damages fetal lung structure and function, causing pulmonary vascular endothelial damage and pulmonary hypoplasia; this results in severe respiratory failure in infants (21-23). In addition, Aikio et al. (24) reported that PROM impaired NO production and reduced sensitivity to NO in extremely preterm infants.

5.3. Congenital Lung Developmental Abnormalities or CDH

Our results confirmed those of previous researches, which reported higher mortality risk due to PPHN attributable to congenital lung developmental abnormalities or CDH, which was consistent with the findings of Nakwan et al. (3) and Mat Bah et al. (10). However, in our study, the number of cases with combined pulmonary developmental abnormalities/CDH was small (n = 4). Future studies with larger sample sizes are warranted, which may also explain the large interval (95% CI 1.088 - 147.068) for the OR of this group.

5.4. Respiratory Distress Syndrome

The incidence of PPHN was significantly higher in preterm infants with RDS (25, 26), and this study demonstrated that RDS was also an independent

Table 2. Death-related Factors due to Persistent Pulmonary Hypertension

Related Factors	Adjusted Odds Ratio	95% Confidence Interval
Cesarean delivery	0.289	0.104 - 0.803
PROM	4.032	1.32 - 12.32
Congenital pulmonary developmental abnormalities /CDH	12.65	1.088 - 147.068
RDS	4.802	1.512 - 15.251
iNO	12.377	3.22 - 47.576
Norepinephrine	2.891	1.03 - 8.118

Abbreviations: PROM, premature rupture of membranes; CDH, congenital diaphragmatic hernia; RDS, respiratory distress syndrome; iNO, inhaled nitric oxide.
[a] Note: Gestational age at birth < 34 weeks, cesarean delivery, RDS, sepsis, congenital pulmonary developmental abnormalities/CDH, pneumothorax, severe IVH, PROM, iNO, Millinon, high-frequency ventilation, norepinephrine were included in the binary stepwise logistic regression analysis.

Table 3. Reasons for Cesarean Delivery in the Survival and Non-survival Groups

Indications	Survival Group (n = 90)		Non-survival Group (n = 10)	
	< 34 wk	≥ 34 wk	< 34 wk	≥ 34 wk
Maternal, perinatal factors	13	25	3	2
Scarred uterus	2	15	0	1
Severe pre-eclampsia/ eclampsia	2	1	1	0
Severe intrahepatic cholestasis of pregnancy	1	0	0	0
Suspected pre-rupture of the uterus	0	1	1	0
Placenta previa with/without bleeding	2	3	0	0
PROM	2	0	0	0
Heart disease in pregnancy	1	3	1	0
Combined cerebrovascular disease in pregnancy	2	0	0	0
Failed vaginal labor	0	0	0	1
Cervical insufficiency	1	0	0	0
Advanced maternal age	0	1	0	0
Obesity	0	1	0	0
Cesarean section requested by the mother	0	6	0	1
Fetus and fetal accessories	12	24	0	3
Abnormal fetal position	0	5	0	0
Poor fetal status	2	15	0	1
Twin pregnancies	9	2	0	0
Huge children	0	2	0	1
Rotating placenta	0	0	0	1
Umbilical cord abnormalities	1	0	0	0
Maternal combined with fetal factors	3	7	0	1

determinant of infant mortality. Walther et al. (27) reported that RDS increased pulmonary artery pressure and decreased pulmonary blood flow velocity in newborns and found that the severity of RDS condition was positively associated with the aggravation of PPHN.

5.5. NO Inhalation

Our study revealed that iNO was an independent factor related to high mortality in newborns with PPHN. Although several previous studies reported that iNO improved oxygenation and reduced the need for extracorporeal membrane oxygenation in infants with PPHN, iNO did not significantly improve the prognosis (7,

8, 12, 28, 29). Nakwan et al. (3) reported findings similar to ours. This may be due to the fact that the infants in the non-survival group in this study were more critically ill, had more comorbidities and complications, and, therefore, were more likely to receive iNO treatment.

5.6. Norepinephrine

In this study, norepinephrine was a possible mortality-related factor due to PPHN. Available literature introduces norepinephrine as a positive inotropic agent used for treating PPHN, but its efficacy and safety in neonates, especially preterm infants, is unclear, lacking any evidence from large randomized controlled studies (30). A prospective study on the effects of norepinephrine in 18 neonates with cardiac insufficiency due to PPHN by Tourneux et al. (31) reported that norepinephrine improved the oxygen demand of newborns with PPHN-induced cardiac dysfunction and enhanced body circulation pressure. However, a retrospective study on 48 preterm infants by Rowcliff et al. (32) reported that, although norepinephrine increased blood pressure in preterm infants with cardiovascular disease, mortality was higher in the preterm group who received norepinephrine, and its effect on distant neurodevelopmental impairment was unclear. Unfortunately, we could not confirm whether this was because infants treated with norepinephrine were more severe cases of PPHN or that norepinephrine was indeed a mortality predictor in infants with PPHN due to our retrospective design.

5.7. Limitations

Our study had some limitations. Firstly, the relatively small sample size and retrospective design limited our findings' generalizability. The results may have been influenced by the relatively small sample size and potential selection bias, and further large, prospective, and multicentric studies are warranted to verify our results. However, Guangdong Provincial People's Hospital is a tertiary medical center in China, and its Neonatal Intensive Care Unit (NICU) is one of the regional referral centres for critically-ill neonates in the Guangdong province. Most of the PPHN cases were referred from other hospitals in Guangdong province, which partially reduced the limitations of its being a single-center study. In addition, due to the lack of relevant data and our retrospective design, we could not calculate the oxygenation index and CRIB II score of infants with PPHN to assess the severity of the PPHN condition. Finally, only a short-term outcome (death) was investigated in this study, and further research is needed on follow-up assessment of distant indicators, such as neurodevelopment, bronchopulmonary dysplasia, and retinopathy of prematurity.

5.8. Conclusions

Caesarean delivery with medical indication was an independent protective factor against death in infants with PPHN. PROM, congenital lung developmental abnormalities/CDH, RDS, iNO, and norepinephrine were independent mortality-related factors in newborns with PPHN. These predictors should be seriously considered to promote the survival of newborns with PPHN.

Footnotes

Authors' Contribution: Z.K. and H.A.J. made substantial contributions to conception and design; S.Y.X. and Z.J. were involved in the acquisition of data, analysis, and interpretation of data; Z.M.L. and Z.Y.Q. were involved in drafting the manuscript and critically revising it for important intellectual content; S.X. and L.Y.M. approved the version to be published.

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Data Reproducibility: All data generated or analyzed during this study are included in the published article.

Ethical Approval: This study was approved by the ethics committee of Guangdong Provincial People's Hospital with the ethics number KY-Q-2021-226-01.

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Informed Consent: The requirement of informed consent was waived due to the retrospective design.

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Table 1. Basic Characteristics and Comparison of the PPHN Survival and Non-survival Groups [a]

Variables	Total (n = 161)	Survival Group (n = 132)	Non-survival Groups (n = 29)	P-Value
Gestational age, wk	37.1 (31.3 - 39.2)	37.36 (33.4 - 39.1)	34.6 (28.7 - 39.4)	0.136
< 34 wk	47 (29.2)	34 (25.8)	13 (44.8)	0.041
Birth weight, g	2700 (1560 - 3250)	2830 (1825-3250)	2100 (1270 - 3100)	0.100
< 2500 g	63 (39.1)	47 (35.6)	16 (55.2)	0.051
Male	111 (68.9)	94 (71.2)	17 (58.6)	0.185
Cesarean delivery	100 (62.1)	90 (68.2)	10 (34.5)	0.001
Twin birth	20 (12.5)	16 (12.1)	4 (13.8)	0.755
IVF	13 (8.2)	8 (6.2)	5 (17.2)	0.065
History of asphyxia	88 (54.7)	69 (52.3)	19 (65.5)	0.195
PPHN primary and perinatal diseases				
Neonatal pneumonia	64 (39.8)	53 (40.2)	11 (37.9)	0.825
Transient tachypnea of the newborn	3 (1.9)	3 (2.3)	0 (0)	1.000
RDS	64 (39.8)	47 (35.6)	17 (58.6)	0.022
Neonatal infections	15 (9.3)	14 (10.6)	1 (3.4)	0.311
Intrauterine infection	62 (38.5)	48 (36.4)	14 (48.3)	0.233
Neonatal amniotic fluid aspiration syndrome	9 (5.6)	9 (6.8)	0 (0)	0.365
MAS	12 (7.5)	10 (7,6)	2 (6.9)	1.000
Sepsis	35 (21.7)	22 (16.7)	13 (44.8)	< 0.001
Asphyxia	33 (20.5)	25 (18.9)	8 (27.6)	0.296
Fetal blood transfusion	2 (1.2)	2 (1.5)	0 (0)	1.000
IUGR/SGA age	18 (11.2)	16 (12.1)	2 (6.9)	0.533
Macrosomia	4 (2.5)	3 (2.3)	1 (3.4)	0.552
Congenital pulmonary developmental abnormalities [b] /CDH	4 (2.5)	1 (0.8)	3 (10.3)	0.019
Pneumothorax	24 (14.9)	14 (10.6)	10 (34.5)	0.003
Mild IVH[c]	10 (6.2)	10 (7.6)	0 (0)	0.211
Severe IVH[c]	21 (13.0)	13 (9.8)	8 (27.6)	0.028
The size DA, mm (n = 97)	3.37 ± 1.18	3.45 ± 1.22	3.04 ± 0.99	0.075
Basic maternal characteristics and diseases during pregnancy (n = 160)				
Age (n = 137)	31.32 ± 5.04	31.13 ± 5.04	32.26 ± 5.06	0.336
Advanced maternal age (≥ 35 y)	35 (25.5)	26 (22.8)	9 (39.1)	0.102
Adverse maternal history [d] (n = 159)	74 (46.5)	62 (47.3)	12 (42.9)	0.667
Prenatal glucocorticoid use	43 (26.7)	36 (27.3)	7 (24.1)	0.73
Turbid amniotic fluid	32 (19.9)	24 (18.2)	8 (27.6)	0.251
Infections during pregnancy	29 (18.0)	23 (17.4)	6 (20.7)	0.679
PROM	23 (14.4)	13 (9.8)	10 (35.7)	0.001
Abruptio placentae	7 (4.4)	5 (3.8)	2 (7.1)	0.354
Placenta previa with/without bleeding	10 (6.3)	9 (6.8)	1 (3.6)	1.000
Gestational diabetes mellitus	33 (20.6)	26 (19.7)	7 (25.0)	0.529
Hypertension during pregnancy	11 (6.9)	9 (6.8)	2 (7.1)	1.000

Treatment				
iNO	17 (10.6)	8 (6.1)	9 (31.0)	< 0.001
Sildenafil	40 (24.8)	31 (23.5)	9 (31.0)	0.394
Milrinon	79 (49.1)	58 (43.9)	21 (72.4)	0.005
Pulmonary surfactants	71 (44.1)	54 (40.9)	17 (58.6)	0.082
High-frequency ventilation	88 (54.7)	67 (50.8)	21 (72.4)	0.034
ECMO	6 (3.7)	4 (3.0)	2 (6.9)	0.295
Dopamine	110 (68.3)	86 (65.2)	24 (82.8)	0.065
Dobutamine	65 (40.4)	53 (40.2)	12 (41.4)	0.903
Norepinephrine	49 (30.4)	35 (26.5)	14 (48.3)	0.021

Abbreviations: MAS, meconium aspiration syndrome; IUGR/SGA, intrauterine growth restriction or small for gestational age infant; DA, ductus arteriosus; iNO, NO inhalation.
[a] Data are expressed as mean ± SD or No. (%).
[b] Pulmonary developmental abnormalities: Including pulmonary hypoplasia and pulmonary dysplasia (there were three cases, two with a congenital diaphragmatic hernia and one with pulmonary vascular malformation).
[c] Mild IVH: Grade I and II of IVH are mild-IVH, and grade III and IV of IVH are severe-IVH.
[d] Adverse maternal history included: Spontaneous abortion, induced abortion, and stillbirth.