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ARTICLE

Survival and associated risk factors for mortality among infants with persistent pulmonary hypertension of the newborn in Malaysia

Mohd Nizam Mat Bah[1] · Racine Yuh Hwa Tan[1] · Hasliza Razak[1] · Mohd Hanafi Sapian[1] · Nisah Abdullah[1] · Emieliyuza Yusnita Alias[1]

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Abstract

Objective This study aims to determine the immediate outcome of persistent pulmonary hypertension of the newborn (PPHN) and risk factors for mortality in the era of inhaled nitric oxide (iNO).

Study design This observational cross-sectional study includes 195 confirmed PPHN with a gestational age of ≥34 weeks without congenital heart disease. Multivariable logistic regression was used to identify risk factors for mortality.

Results The mortality rate was 16.4%, with the highest mortality with pulmonary hypoplasia. Of 195, 65% received iNO; 18% were iNO non-responders with the majority having pulmonary hypoplasia. Independent risk factors for mortality were the presence of reversal of flow at the descending aorta, pulmonary hypoplasia, APGAR scores ≤ 5 at 5 min, and idiopathic PPHN with an adjusted odds ratio of 15.9, 7.5, 6.7, and 6.4, respectively.

Conclusions Despite the usage of iNO, mortality due to PPHN remains high and is related to etiology and cardiac function.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a complex disorder, occurring at a rate of 0.5 to 6 per 1000 live births (LB) [1]. It results from the failure of transition from fetal to postnatal circulation leading to persistent elevation of pulmonary resistance and can be due to primary or secondary lung problems [2]. PPHN caused by lung vasculature changes is thought to be short term and reversible, while conditions such as lung hypoplasia are long term that may lead to persistent effects on child health [3].

Despite advances in the management of PPHN in the current era, the overall mortality is still high, ranging between 7 and 39% [1, 3–6]. In addition to the usual general management principles of ill neonates, severe forms of PPHN may require specific treatment modalities that may not be readily available in lower-and-middle income countries (LMIC). This includes lung recruitment using conventional and high-frequency oscillatory ventilation (HFOV), the use of pulmonary and systemic vasodilators such as inhaled nitric oxide (iNO) [7], sildenafil [8], milrinone [9], and extracorporeal membrane oxygenation (ECMO) [10].

Careful evaluation of associated risk factors for mortality should be able to assist neonatologists or pediatricians in deciding the proper treatment for PPHN. This includes the use of comprehensive 2d-echocardiography to make the diagnosis of PPHN and to exclude structural congenital heart disease (CHD). Moreover, 2d-echocardiography should be used as an evaluating tool for assessing the severity of PPHN, extrapulmonary shunt, myocardial function, and iNO response [11–13]. This will give real-time, rapid, and reliable information to tailor to the PPHN management. Hence, the goals of this study are to determine the immediate outcome and associated risk factors for mortality of PPHN in LMIC.

Materials and methods

This retrospective cross-sectional study was conducted in a multidisciplinary, level III, 22-bedded Neonatal Intensive Care

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✉ Mohd Nizam Mat Bah
nurnizam95@gmail.com

[1] Department of Pediatrics, Hospital Sultanah Aminah, Ministry of Health, Johor Bahru, Malaysia

Unit (NICU), Hospital Sultanah Aminah Johor Bahru (HSAJB), Johor, Malaysia. The annual birth rate for HSAJB is about 13,000 LB per year, and for the state of Johor is about 50,000 LB per year. Approximately 600 infants were admitted each year to the NICU, with 75% being medical cases.

All neonates (inborn and outborn admissions) with a gestational age of ≥34 weeks with 2d-echocardiographically confirmed PPHN from January 2013 to December 2018, were included in this study. During this study period, there is no dedicated neonatologist in the NICU; all cases of PPHN were managed by a general pediatrician assigned to the NICU yearly and supervised by a senior pediatric cardiologist following a local standard written guideline on PPHN, HFOV, and iNO [14]. Briefly, all patients received sedation unless it is contraindicated. Inotropes were given if there was any sign of hypotension or cardiac dysfunction. Notably, 2d-echocardiography must be performed in all suspected PPHN or before commencement of HFOV. In this study, iNO was used early, and not as rescue therapy depending on the clinical presentation and etiology of PPHN. iNO responder is defined if patients showed either an increase in PaO2 > 20 mmHg from the baseline, increase in post ductal saturation by 10%, able to drop Fio2 by 0.2, or if there is a significant reduction in right to left shunt with an improved cardiac function by 2d-echocardiogram (Supplement 1). There was no ECMO available during the study. Adherence to this guideline were monitored by having monthly PPHN reviews (2013–2016) and three monthly (2017–2018) at the department level. Meanwhile, all mortality cases were discussed within 7 days of mortality.

All infants less than 72 h of life with suspected PPHN had a complete transthoracic 2d-echocardiography (TTE). The echocardiography was performed by certified medical personnel in pediatric and congenital heart disease using Applio 300 ultrasound system with 5 Mhz neonatal probe (Toshiba Corp., Otawara-shi, Tochigi, Japan). All images were stored in the 2d-echocardiography archiving system (Syngo@siemens, USA) for reviewing and verification of diagnosis by a pediatric cardiologist.

The diagnosis of PPHN was made if there was either bidirectional or continuous right to left shunt across the foramen ovale (FO) or ductus arteriosus (DA) with no CHD [1]. PPHN was categorized into severe and non-severe using 2d-echocardiography features, as described by Rhoofthooft et al. [4]. Briefly, severe PPHN is defined if there was a continuous right to left shunt across the DA or FO, and non-severe PPHN if there was a bidirectional shunt. Other 2d-echocardiography features of PPHN such as dilated right atrium, dilated right ventricle, presence of mitral regurgitation, myocardial dysfunction, the peak pressure gradient across of tricuspid valve and color doppler of reversal of flow at the descending aorta were recorded. In addition, other causes of reversal of flow at the descending aorta were excluded (hemitruncus, large coronary fistula, or severe aortic regurgitation).

Significant CHD or acquired heart disease, which may give similar features of PPHN, such as total anomalous pulmonary venous drainage, severe coarctation of the aorta, cyanotic CHD, or severe cardiomyopathy were excluded from this study. Infants who had 2d-echocardiography for acute hypoxic respiratory failure after 72 h of life were excluded.

PPHN data was retrieved from the PPHN Clinical Information System. This clinical database was developed in 2012 to monitor the performance and outcome of infants with PPHN who received HFOV and iNO. Therefore, detailed data such as mean airway pressure, FiO2, PaO2, and PaCO2 were not collected and entered in the clinical registry. Data were entered at the time of diagnosis and regularly updated until the patient was discharged or died. Data retrieved include demographic data (ethnicity, gender, gestational age, APGAR score, method and place of delivery, chest compression at birth), ventilator strategies (conventional or HFOV), iNO usage, the etiology of PPHN, 2d-echocardiography features of PPHN, immediate outcome, and hospital length of stay.

The etiology of PPHN in a patient with two or more possible causes was classified according to the hierarchy, based on the likelihood of the condition to cause PPHN as described by Steurer et al. [3]. The possible etiologies are congenital diaphragmatic hernia (CDH), other congenital malformations of the respiratory system, meconium aspiration syndrome (MAS), infection/sepsis, hypoxic-ischemic encephalopathy (HIE), and respiratory distress syndrome (RDS). Patients with CDH, Potter syndrome, or oligohydramnios were grouped as having pulmonary hypoplasia. Idiopathic PPHN is defined if PPHN occurred without any known etiologies. Infants with trisomy 21 who did not have MAS, HIE, or infection were considered to have primary PPHN.

This study was registered with the National Malaysian Research Registry (NMRR-17-790-34839) and approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia. The ethics committee waived informed consent.

Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY, USA). Means or medians were used to describe continuous variables, while frequencies and percentages were used for categorical variables. Group comparisons were made using Pearson chi-square or Fisher's exact test when any expected cell count was < 5 for categorical data. A linear regression analysis was used to analyze the trend in mortality rate over time. A p value < 0.05 represented a statistically significant result.

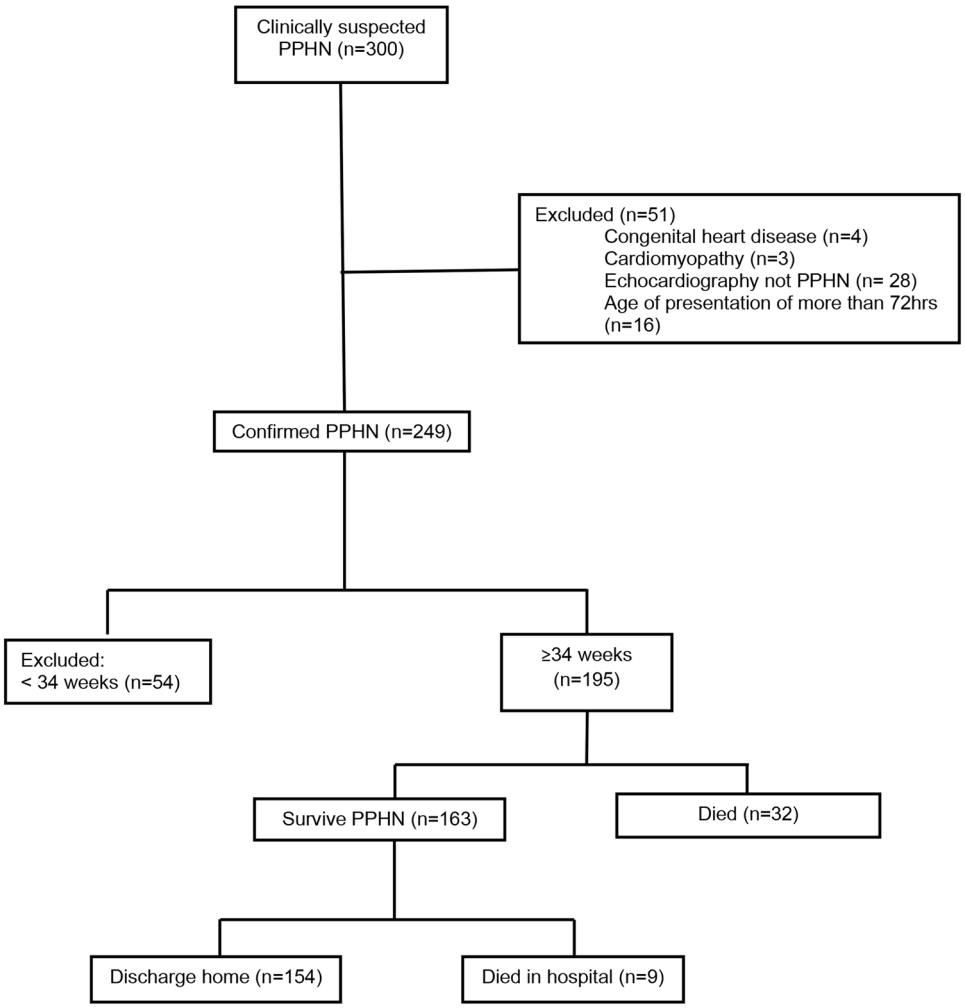

Fig. 1 Study population and immediate outcome. PPHN, Persistent pulmonary hypertension of the newborn.

Univariable and multivariable binary logistic regression were used to identify risk factors for poor outcomes. Factors included in the binary logistic regression analysis were demographic data, PPHN etiology and echocardiography features. Factors excluded from the regression were PPHN severity, inotropes and iNO usage. PPHN severity was excluded from logistic regression to avoid multicollinearity as severity was derived from echocardiography features. Meanwhile, inotropes and iNO usage were excluded as we considered inotropes and iNO usage as treatments for PPHN rather than possible risk factors for poor outcome. The crude odds ratio (OR) and adjusted odds ratio were calculated, and an OR was considered significant if the 95% confidence interval (CI) excluded one.

Results

There were 82,915 LB, and 3997 infants (inborn and outborn) admitted into the NICU over the 6-year study period. Of the 3997, 195 (4.9%) met the study criteria of PPHN (Fig. 1). Of 195, 172 were inborn admissions giving an incidence of PPHN of 2.07 (95% CI:1.76 to 2.38) per 1000 LB. The mean birth weight and gestational age were 2.9 ± 0.5 kg and 38.8 ± 1.7 weeks, respectively. Diagnosis of PPHN was made within 24 h of life in 180 (92.3%), 13 (6.7%) between 24 and 48 h and two (1.0%) between 48 and 72 h. Inotropic support was given in 108 (55.4%) PPHN patients.

Table 1 shows the characteristics and comorbidities of survivors and non-survivors of infants with PPHN. APGAR scores < 5 at 1-min were noted in 26.1% (20 MAS, nine pulmonary hypoplasia, eight HIE, five pneumonias, four RDS, three idiopathic, and two primary PPHN). Meanwhile, APGAR scores of < 5 at 5-min were noted in 12.8% (ten MAS, five HIE, four pulmonary hypoplasia, three RDS, two idiopathic, and one pneumonia). There was a statistically significant difference between PPHN survivors and non-survivors in both APGAR score less than five at 1-min and at 5-min after delivery.

Table 1 The characteristics of survivors and non-survivors of infants with persistent pulmonary hypertension of the newborn in Hospital Sultanah Aminah, Johor Bahru, Malaysia 2013–2018.

Variables	Total *N* (%)	Outcome		*p* value
		Survivor, *N* †(%)	Non-survivor, *N* †(%)	
Race				
Malay	143 (73.3)	115 (80.4)	28 (19.6)	0.10
Non-Malay	52 (26.7)	48 (92.3)	4 (7.7)	
Sex				
Female	78 (40.0)	63 (80.8)	15 (19.2)	0.38
Male	117 (60.0)	100 (85.5)	17 (14.5)	
Birth weight (kg)				
1.5–2.49	51 (26.2)	42 (82.4)	9 (17.6)	0.78
>2.5 kg	144 (73.8)	121 (84.0)	23 (16.0)	
Gestational age (week)				
34–37	38 (19.5)	33 (86.8)	5 (13.2)	0.55
>37	157 (80.5)	130 (82.8)	27 (17.2)	
Method of delivery				
LSCS	112 (57.4)	96 (85.7)	16 (14.3)	0.35
SVD	83 (42.6)	67 (80.7)	16 (19.3)	
Place of delivery				
Inborn	172 (88.2)	145 (84.3)	27 (15.7)	0.46
Outborn	23 (11.8)	18 (78.3)	5 (21.7)	
APGAR score at 1 min				
Less than 5	51 (26.2)	36 (70.6)	15 (29.4)	**0.004**
More than 5	144 (73.8)	127 (88.2)	17 (11.8)	
APGAR score at 5 min				
Less than 5	25 (12.8)	14 (56.0)	11 (44.0)	**<0.001**
More than 5	170 (87.2)	149 (87.6)	21 (12.4)	
Chest compression	11 (5.6)	7 (63.6)	4 (36.4)	0.07
PPHN severity				
Severe	125 (64.1)	94 (75.2)	31 (24.8)	**<0.001**
Moderate	70 (35.9)	69 (98.6)	1 (1.4)	
Pneumothorax	43 (22.1)	40 (93.0)	3 (7.0)	0.06
Total	195 (100.0)	163 (83.6)	32 (16.4)	

PPHN persistent pulmonary hypertension of the newborn, *LSCS* lower segment cesarian section, *SVD* spontaneous vaginal delivery.

(%) represents the percentage of the total PPHN.

†(%) represents the percentage of variables.

Significant difference if *p* value < 0.05 (in bold).

There were 125 (64%) severe PPHN, with statistically significant mortality observed in the severe PPHN group compared to non-severe PPHN (24.8% vs. 1.4%, $p < 0.001$).

Of 195 PPHN, 68 (34.9%) received conventional ventilation only, 112 (57.4%) had initial conventional mechanical ventilation followed by HFOV, and 15 (7.7%) received HFOV as initial ventilation. The median duration of HFOV was three days (IQR 1.8–4.0 days) with the longest duration of 16 days. Of 195 PPHN, 126 (64.6%) received iNO with a median duration of two days (IQR 1.0–3.0 days) with the longest duration of 11 days. Of 126 who received iNO, 28 (22.2%) were given via conventional ventilation and 71 (56.3%) were severe PPHN. Overall, there were 89 (70.6%) iNO responders, 14 (11.1%) partial responders, and 23 (18.2%) iNO non-responders. All non-responders did not survive PPHN, with a median age of death of one day (IQR 1–2 days). All full and partial iNO responders survived the PPHN, but six (three from each group) died before discharge from the hospital. Of 14 partial iNO responders, adjunct therapy with sildenafil was given in three patients. The majority of non-responders were related to pulmonary hypoplasia ($n = 9$, 39.1%) and idiopathic PPHN ($n = 3$, 13.0%).

The leading causes of PPHN were MAS, followed by pneumonia and pulmonary hypoplasia (Table 2). Of the 20 with pulmonary hypoplasia, 14 were associated with CDH, two each for oligohydramnios and dysmorphic infant, and one each for severe right lung eventration and hydrops fetalis. The highest mortality rate was observed in PPHN related to pulmonary hypoplasia (55.0%) and idiopathic PPHN (33.3%). In PPHN related to pulmonary hypoplasia, a statistically significantly higher mortality rate was noted in those who received iNO compared to those who did not, 90% vs. 20%, $p < 0.01$ (Table 2). Further analysis shows that PPHN related to pulmonary hypoplasia has poor outcomes in the first four years of the study compared to the last 2 years, with a mortality rate of 88.9% vs. 27.3%, $p = 0.02$.

Table 3 shows the 2d-echocardiography features of PPHN among survivors and non-survivors. Of 195 PPHN, 65 (33.3%) had myocardial dysfunction, 48 (24.6%) had a reversal of flow at the descending aorta, and continuous right to left shunt through the FO and DA in 78 (40.0%) and 99 (50.7%), respectively. Of 65 with myocardial dysfunction, four patients had trivial aortic regurgitation (AR), and none had significant AR. Forty-two (64.6%) patients with myocardial dysfunction had similar etiology with those of reversal of flow (11 pulmonary hypoplasia, ten pneumonia, seven MAS, four each for idiopathic and primary PPHN, three HIE, two infection and one RDS). Further analysis shows that there was a statistically significant reversal of flow at the descending aorta in patients with myocardial dysfunction compared to those with no myocardial dysfunction (42/65 [64.6%] vs. 6/130 [4.6%], $p < 0.001$). Univariable analysis shows a statistically significant difference between survivors and non-survivors in infants with myocardial dysfunction, a reversal of flow at the descending aorta, and shunt across the DA (Table 3).

Mortality related to PPHN was 16.4% (95% CI: 11.6% to 22.5%), with no significant changes over the study period,

Table 2 The etiology-specific mortality rate of persistent pulmonary hypertension of the newborn and its relationship with inhaled nitric oxide.

Etiology	All PPHN		With iNO		Without iNO		*p* value
	Total, *N* (%)	Mortality, *n* (%)	Total, *n*	Mortality, *n* (%)	Total, *n*	Mortality, *n* (%)	
MAS	64 (32.8)	5 (7.8)	50	4 (8.0)	14	1 (7.1)	1.00
Pneumonia	43 (22.0)	3 (7.0)	24	3 (12.5)	19	0 (0.0)	0.24
Pulmonary hypoplasia	20 (10.3)	11 (55.0)	10	9 (90.0)	10	2 (20.0)	**<0.01**
HIE	19 (9.7)	3 (15.8)	12	2 (16.7)	7	1 (14.3)	1.00
Idiopathic	15 (7.7)	5 (33.3)	9	3 (33.3)	6	2 (33.3)	1.00
RDS	14 (7.2)	2 (14.3)	7	0 (0.0)	7	2 (28.6)	0.46
[†]Primary	13 (6.7)	2 (15.4)	8	1 (12.5)	5	1 (20.0)	0.64
Infection	7 (3.6)	1 (14.3)	6	1 (16.7)	1	0 (0.0)	1.00
All	195 (100.0)	32 (16.4)	126	23 (18.3)	69	9 (13.0)	0.35

iNO inhaled nitric oxide, *PPHN* persistent pulmonary hypertension of the newborn, *RDS* respiratory distress syndrome, *MAS* meconium aspiration syndrome, *HIE* hypoxic-ischemic encephalopathy.

(%) represents the percentage of all PPHN.

[†]Related to trisomy 21.

Significant difference if p value < 0.05 (in bold).

Table 3 2d-echocardiography features of persistent pulmonary hypertension of the newborn among survivors and non-survivors.

Echocardiography features	Total PPHN *N* (%)	Outcome		*p* value
		Survivors *n* [†](%)	Non-survivors *n* [†](%)	
Dilated RA and RV				
Yes	181 (92.8)	150 (82.9)	31 (17.1)	0.47
No	14 (7.2)	13 (92.9)	1 (7.1)	
Shunt across the FO				
Continuous right to left	78 (40.0)	62 (79.5)	16 (20.5)	0.30
Bidirectional, dominant right to left	109 (55.9)	95 (87.1)	14 (12.9)	
Bidirectional, dominant left to right	8 (4.1)	6 (75.0)	2 (25.0)	
Shunt across the DA				
Bidirectional, dominant right to left	96 (49.2)	93 (96.9)	3 (3.1)	**<0.001**
Continuous right to left	99 (50.8)	70 (70.7)	29 (29.3)	
Presence of myocardial dysfunction				
Yes	65 (33.3)	39 (60.0)	26 (40.0)	**<0.001**
No	130 (66.7)	124 (95.4)	6 (4.6)	
Presence of reversal of flow at the DAo				
Yes	48 (24.6)	24 (50.0)	24 (50.0)	**<0.001**
No	147 (75.4)	139 (94.6)	8 (5.4)	
Presence mitral regurgitation				
Yes	96 (49.2)	76 (79.2)	20 (20.8)	0.10
No	99 (50.8)	87 (87.9)	12 (12.1)	
[a]Peak PG across the TV, Mean ± SD (mmHg)	37.7 ± 18.9	37.1 ± 18.8	40.5 ± 19.1	0.39
Total	195 (100)	163 (83.6)	32 (16.4)	

PPHN persistent pulmonary hypertension of the newborn, *RA* right atrium, *RV* right ventricle, *TV* tricuspid valve, *FO* foramen ovale, *DA* ductus arterious, *DAo* descending aorta, *PG* pressure gradient, *SD* standard deviation.

(%) represents the percentage of the total PPHN.

[†](%) represents the percentage of total echocardiography features.

[a]13 with no documented tricuspid regurgitation.

Significant difference if p value < 0.05 (in bold).

Table 4 Risk factors for mortality in infants with persistent pulmonary hypertension of the newborn.

Variable	Total	Died, *n* (%)	Crude OR (95% CI)	*p* value	[a]Adjusted OR (95% CI)	*p* value
Echocardiography features						
Reversal of flow at the DAo	48	24 (50.0)	17.37 (6.99, 43.16)	<0.001	15.91 (5.64, 44.92)	<0.001
Continuous right to left shunt at the DA	99	29 (29.3)	12.84 (3.76, 43.87)	<0.001	–	
Myocardial dysfunction	65	26 (40.0)	13.78 (5.29, 35.91)	<0.001	–	
APGAR score						
<5 at 5 min	25	11 (44.0)	5.58 (2.24, 13.88)	<0.001	6.72 (2.04, 22.15)	0.002
<5 at 1 min	51	15 (29.4)	3.11 (1.42, 6.84)	0.005	–	
PPHN etiology						
Idiopathic	15	5 (33.3)	2.83 (0.89, 8.94)	0.076	6.46 (1.52, 27.43)	0.011
Pulmonary hypoplasia	20	11 (55.0)	8.96 (3.32, 24.17)	<0.001	7.40 (2.04, 26.89)	0.002

Odds ratios are considered to statistically significantly different from the reference category if their 95% confidence intervals exclude one.

CI confidence interval, *OR* odds ratio, *PPHN* persistent pulmonary hypertension of the newborn, *DAo* descending aorta, *DA* ductus arteriosus.

[a]Analyzed with multivariable binary logistic regression, Enter Method, corrected for the race, sex, and gestational age.

$p = 0.52$ (Supplement 2). The median age of death related to PPHN occurred at one day of life (Q1 1, Q3 2). Of 163 who survived PPHN, nine died before hospital discharge (five trisomy 21, two CDH, one each for severe HIE and dysmorphic infant). The causes of death were related to infection with median age of death of 11 days (Q1 8, Q3 58). Therefore, the in-hospital mortality was 21%. The median length of stay for PPHN survivors was 13 days (Q1 10, Q3 20).

Table 4 shows the crude and adjusted OR for mortality. The independent risk factors for mortality were a reversal of flow at the descending aorta (aOR = 15.9), PPHN due to pulmonary hypoplasia (aOR=7.5), APGAR score less than five at 5 min (aOR = 6.7), and idiopathic PPHN (aOR = 6.4).

Discussion

PPHN is associated with high mortality and morbidity [15]. In this study, iNO was used in selected cases of PPHN after a full assessment with 2d-echocardiogram and optimization of ventilation and hemodynamic. However, the mortality rate (16%) related to PPHN in this study is still high, without any statistically significant changes over time. Nonetheless, the mortality rate is within the higher-end range of high-income countries which ranges between 7 and 15% [15] and lower-end range of other Asian countries with a mortality rate of 12–40% [5, 6, 16, 17]. Low mortality in this study compared to other Asian countries could be due to availability of iNO, strict adherence to local practice guidelines, continuous monitoring of the performance and outcome of PPHN with clinical registry, followed by changes in practice related to iNO usage in our unit. Among significant changes made in 2017 were the reinforcement the iNO guideline, particularly optimization of ventilation and hemodynamic support, as well as cessation of iNO usage in PPHN secondary to CDH. These changes have led to less mortality in PPHN related to CDH in the last two years of the study. Other changes were the introduction of oral sildenafil to partial iNO responders. Initial results show some improvement in oxygenation. However, due to a small number of patients, this result is difficult to interpret. Nevertheless, this result illustrates that in LMIC, despite lacking in dedicated neonatologists and ECMO, a good outcome is possible with continuous monitoring using clinical database and adherence to the proper standardized guideline.

Previous randomized controlled trials showed that up to one-third of PPHN do not respond to iNO [18, 19]. However, only one-fifth fails with iNO in this study. A lower rate of iNO non-responders could be due to the highly selective criteria for iNO or early usage of iNO. Nevertheless, the management of iNO non-responders is challenging in centers without ECMO services. Sildenafil has been recommended as an adjunct therapy in infants who are refractory to iNO [20]. In a recent meta-analysis, Kelly et al. [8] noted that sildenafil might reduce mortality and improve oxygenation. Therefore, where ECMO or iNO is not readily available, sildenafil is the alternative treatment. In addition to sildenafil, milrinone has been shown to improve oxygenation in severe PPHN [9] and is recommended in PPHN with myocardial dysfunction [20].

Currently, TTE is a standard practice to assess myocardial function in ill neonates [13]. Several TTE markers have been identified to be associated with myocardial dysfunction [11, 21, 22]. However, except for shunts across the DA, other indices are exceedingly difficult to attain in daily practice. Furthermore, high-end 2d-echocardiography machines may not be readily available in LMIC. Therefore, there is a need to search for a simple 2d-echocardiography marker for myocardial dysfunction. In this study, TTE was used to

detect the presence of a reversal of flow at the descending aorta. TTE is reliable and has been used to assess the reversal of flow at the descending aorta in a neonate with CHD [23] and premature infant [24]. This study shows that the presence of a reversal of flow at the descending aorta is shown to be a significant 2d-echocardiography predictor associated with mortality. It may represent a severe left ventricular dysfunction where the cardiac output is very minimal, leading to a reversal of flow. Due to low mortality in their cohort, Peterson et al. [21] failed to show that reversal of flow at the descending aorta as an indicator for mortality. Hence, these simple methods with color Doppler interrogation at the ascending, transverse, and descending aorta should be part of the routine use of 2d-echocardiography in PPHN [13].

Knowledge of associated risk factors for mortality is essential to guide the management of PPHN. Numerous studies have shown that severe PPHN [15, 25], myocardial dysfunction [21], and continuous right to left shunt through the patent DA [12] are associated with poor outcome. However, in this study, presence of myocardial dysfunction and continuous right to left shunt across the DA (severe PPHN) is significantly associated with mortality in univariable but not in the multivariable analysis. This could be due to better management in this group of patients or due to the inclusion of reversal flow (a severe myocardial dysfunction) in the regression model, which may influence the analysis.

In addition to the reversal of flow at the descending aorta, etiology of PPHN were also associated with poor outcome. This study shows that patients with pulmonary hypoplasia and idiopathic PPHN are six to seven times more likely to die compared to their counterparts. This result correlates with the previous study, which shows that PPHN related to pulmonary hypoplasia is associated with high mortality [3, 26]. In addition, there was no statistically significant difference in mortality rate between iNO and no iNO group. This was due to a high mortality rate in patients with pulmonary hypoplasia who received iNO compared to no iNO. High mortality may suggest that iNO is not beneficial and may instead cause a detrimental effect in PPHN related to CDH. This finding is not surprising and correlates well with the finding by Putnam et al. [27], which shows that iNO usage in CDH is associated with higher mortality. Therefore, iNO should not be used routinely without proper assessment [20, 28, 29]. Optimization of lung volume with HFOV and cardiac output with inotropes should be the focus in the initial management of CDH with PPHN.

Another significant risk factor for mortality identified in this study was the APGAR score at 5-min. Infants with APGAR score less than five at 5-min are six times more likely to die compared to those with more than five. Poor APGAR score at 5 min can occur in severe HIE and severe MAS. This result correlates with previous studies [17, 25] and highlights the importance of good perinatal care and resuscitation of the newborn at birth. Therefore, the overall improvement of perinatal care may reduce the mortality rate related to PPHN.

Limitation of the study

There are a few limitations to this study. Firstly, 2d-echocardiography was conducted by scores of trained echocardiographers, and a single pediatric cardiologist reviewed all images. This may lead to inter-operator variability, and bias may occur during the interpretation. Therefore, as a reversal of flow at the descending aorta is an important marker for PPHN mortality, further study is needed to assess the inter-observer reliability.

Secondly, under-reporting of myocardial dysfunction may occur. In clinical practice, a stabilization of ill infants with inotropes, correction of acidosis, and fluid resuscitation is a priority before 2d-echocardiogram. This may improve the myocardial dysfunction leading to under-reporting. Furthermore, lack of high-end echocardiography machines in the NICU, which can measure various indices of myocardial dysfunction, may also lead to under-reporting.

Thirdly, 2d-echocardiography features rather than oxygen index (OI) were used to assess the severity of PPHN. 2d-echocardiography is preferred due it being non-invasive and giving real-time information on the shunt and function. In contrast with 2d-echocardiogram, OI results can be influenced by ventilator settings and may vary with different sites of arterial access [30]. However, the advantages of OI is that it can categorize the severity of PPHN into many grades; moderate, severe, and very severe [31]. Therefore, further study is needed to correlate the 2d-echocardiography features (shunt across the DA, FO, and reversal of flow) with OI to determine the grading of PPHN severity.

Conclusions

The mortality of PPHN is still high in the current era of iNO, especially with iNO non-responders, pulmonary hypoplasia, and idiopathic PPHN. Hence, further study is needed to improve the PPHN outcome in this group of infants.

This is the first study that shows the reversal of flow at the descending aorta is a significant associated risk factor for mortality. It is a simple echocardiography marker that indicates severe myocardial dysfunction.

As poor APGAR score at 5-min and cardiac function are associated with poor outcome, improvement in perinatal, post-delivery care, and optimization of hemodynamics may help reduce PPHN mortality.

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Author contributions MNMB conceptualized and designed the study, analyzed the data, drafted the initial manuscript, reviewed, and revised the final manuscript. RTYH, MHS, HR, and NA were involved in study design, data collection, data analysis, and drafted the initial manuscript. EYA was involved in the study design, critically reviewed the manuscript, and revised the final document. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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