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Red Cell Distribution Width (RDW) - An Early Predictor of Persistent Pulmonary Hypertension of Newborn (PPHN): A Comparative Study in Dhaka, Bangladesh

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Abstract: Objective: Early diagnosis of Persistent pulmonary hypertension of newborn is a challenge in developing countries. This study aimed to observe the association of Red Cell Distribution Width (RDW) in this critical condition of neonates. Method: This retrospective study was performed in Neonatology department of United Hospital Limited, Dhaka, over 5 years (2013 to 2017) where all PPHN cases were enrolled and compared with neonates without having PPHN. Pre-formed questionnaire was used to collect data. Baseline complete blood count was reviewed in all cases to see the mean Red Cell Distribution Width (RDW). Risk factors for developing persistent pulmonary hypertension was analyzed and cut off value of RDW was observed using Receiver-operating characteristics (ROC) curve. Result: A total of 157 cases were found with PPHN having male predominance (66%). Important risk factors for PPHN were maternal pregnancy induced hypertension and asthma. Respiratory Distress Syndrome and Meconium Aspiration Syndrome were strongly associated with PPHN. RDW was found higher in PPHN neonates than those in the control group ($p < 0.05$). The cutoff point of RDW predictive of PPHN was 17.05 (with 85% sensitivity). Conclusion: Red Cell Distribution Width is an early predictor of persistent pulmonary hypertension of Newborn.

Keywords: Persistent Fetal Circulation, RDW, Predictor, PPHN, Bangladesh

1. Introduction

Persistent pulmonary hypertension of newborn (PPHN) is a commonly encountered condition during neonatal period. This occurs as a consequence of failed pulmonary vascular transition at birth and leads to pulmonary hypertension with shunting of deoxygenated blood across the foramen ovale (FO) and patent ductus arteriosus (PDA) [1, 2]. Subsequently it leads to severe hypoxemia and life-threatening circulatory failure.

PPHN has been reported to be a frequent cause of hypoxemic respiratory failure in term and late preterm infants affecting 0.43 to 6.8 per 1000 live births. But the incidence is likely to be higher in developing countries than developed ones [3]. It contributes up to 10% of neonatal intensive care unit admission and reported mortality rate ranges from 4 to 33% and 7– 20% of the survivors develop long term impairments such as hearing deficit, chronic lung disease and intracranial bleed [4, 5].

There are several risk factors for this condition including antenatal and perinatal factors of mothers as well as neonates. Maternal pregnancy induced hypertension and pre-eclampsia,

gestational diabetes, asthma, infections, neonatal diseases like respiratory distress syndrome, perinatal asphyxia, meconium aspirations, pneumonia, congenital heart diseases etc. are some well- established factors contributing to PPHN [6-9].

The newborns are either ill at the delivery room or manifest within 12-24 hours of life. The classic clinical presentation includes respiratory distress, cyanosis, hypoxemia and acidosis. But the diagnosis of PPHN should be suspected when the level of hypoxemia is disproportionate to the degree of respiratory distress and radiological findings. Most of the time, it needs clinical expertise to suspect PPHN based on risk factors and these clinical presentations [10-12].

Echocardiogram is the gold standard for diagnosis of PPHN. But it is not available in all settings. There are some other tools for supporting the diagnosis of PPHN such as arterial blood gas, chest X-ray, pulse oximetry test etc. Among these, red cell distribution width is a newly explored investigation which can be beneficial for predicting PPHN.

The Red Cell Distribution Width (RDW) is a widely available, inexpensive, and highly reproducible test that reflects the range of the red cell sizes. Erythropoietin, a hormone, is primarily responsible for RBC production and maturation in the bone marrow and is a major determinant of the Red Cell Distribution Width (RDW). Abnormal production of erythropoietin and decreased responsiveness to the hormone can lead to an increase in RDW values [13].

RDW is routinely reported in complete blood count and can be raised in anaemia, septicemia, autoimmune disease, cardiac and pulmonary conditions, chronic inflammatory and renal conditions [14]. Though exact pathophysiology is unknown, raised RDW is associated with morbidity, need of mechanical ventilation support and mortality in children and adult population [15-17].

Evidence also suggests that raised RDW is associated with persistent pulmonary hypertension of newborn (PPHN). But limited studies have been performed on PPHN in Bangladesh [7, 18] and even no study done yet to see the correlation between PPHN and raised RDW. So, we aimed this study to find out the relation of RDW in newborns with PPHN. We also tried to find out the risk factors associated with PPHN. This will surely act as a baseline for evaluating PPHN cases with early identification and timely management.

2. Material & Methods

This retrospective study was conducted in the department of Neonatology of United Hospital Limited over a period of five years (January 2013-December 2017). United Hospital is one of the largest private hospitals in the center of Dhaka city, the capital of Bangladesh which is famous for its sophisticated patient care and intensive care services including neonatal intensive care unit. After ethical approval, a pre-formed questionnaire was used to obtain patient information. All admitted neonates having diagnosis of persistent pulmonary hypertension of Newborn (PPHN) confirmed by Echocardiogram, were enrolled as cases. Healthy newborns with non-hemolytic jaundice who were admitted for phototherapy on the second or third day of birth were the control group. The pre-designed questionnaire included baseline variables: gestational age, birth weight of newborns, mode of delivery (normal vaginal delivery or cesarian section delivery) and sex (male or female) etc. Among maternal variables, presence of gestational diabetes (GDM), asthma and pregnancy induced hypertension (PIH) were evaluated. Presence of neonatal disease conditions like respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), transient tachypnea of newborn (TTNB), Congenital pneumonia, perinatal asphyxia etc. were also documented among cases. Neonates having PPHN were again categorized into mild, moderate and severe PPHN based on Echocardiographic standards [6]. Completed blood count results were reviewed to see the values of Red Cell Distribution Width (RDW) of all enrolled neonates; which were sent within first 48 hours of admission. Other investigations and treatment of patients were done according to unit protocol. Risk factors for PPHN were analyzed by using chi square test for qualitative variable and independent t- test for quantitative variables. P value less than 0.05 was considered statistically significant. Multiple logistic regression was also performed to find out the significant risk factor. RDW values were compared between two groups (PPHN vs Non-PPHN). Receiver-operating characteristics (ROC) curve analysis was done to determine the optimal cutoff point of RDW for identifying neonates with PPHN.

3. Results

A total of 157 cases were found with PPHN. It was categorized in figure 1 based on Echocardiogram findings where 57% patients had mild PPHN followed by severe and moderate variety.

Table 1. *Comparison of baseline characteristics in two groups (PPHN vs non-PPHN group).*

Variable	PPHN group N=157 (%)	Non-PPHN group N=160 (%)	P value
Mean gestational age (weeks)	35.6± 2.54	37.1 ± 1.2	0.00
Mean birth weight (g)	2598.22 ± 760.35	2923.19 ± 392.36	0.00
Sex			
Male	103 (66)	74 (46)	0.001
Female	54 (34)	86 (54)	
Mode of delivery			
NVD	16 (10.2)	3 (1.8)	0.001
LUCS	139 (89)	157 (98)	

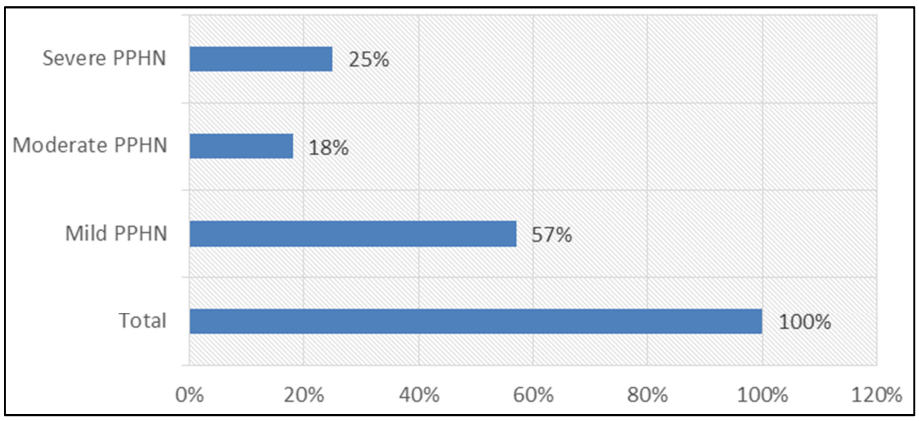

Figure 1. *Distribution of PPHN cases; n=157 (Confirmed by Echocardiogram).*

Table 1 shows comparison of baseline characteristics between case and control group. The Mean gestational age was 35.6 ± 2.54 weeks and mean birth weight was 2598.22 ± 760.353 g among PPHN group which were slightly lower than non-PPHN group and p value was <0.05. Males were predominant (66%) with a male-female ratio of 1.9:1 and 69% were inborn among cases. Most of the newborns were delivered by cesarian section (89%).

Table 2 reveals comparison of maternal variables among these groups where all disease conditions were significantly higher among cases. In table 3, multivariate logistic regression analysis was done to see the association of maternal risk factors with PPHN which revealed that p value was significant for maternal PIH and asthma.

Sub group analysis was also done to see association of PPHN with RDS, MAS, Congenital pneumonia, TTNB, neonatal jaundice and perinatal asphyxia in respect to gestational age (term and pre-term neonates) as shown in figure 2.

Table 2. *Comparison of maternal risk factors.*

Variable	PPHN group N=157 (%)	Non-PPHN group N=160 (%)	P value
PIH	36 (23)	14 (9)	0.000
Asthma	13 (8.2)	02 (1)	0.003
GDM	60 (38)	45 (28)	0.03

Table 3. *Multivariate logistic regression analysis for significant maternal risk factors with PPHN.*

Maternal risk factors	B*	OR**	95% CI***	P value
Maternal PIH	-1.03	0.355	0.18-0.69	0.003
Asthma	-1.71	0.180	0.03-0.83	0.028
GDM	-0.39	0.676	0.41-1.10	0.115

(*β= Beta co-efficient, **OR= Odds Ratio, ***CI= Confidence interval)

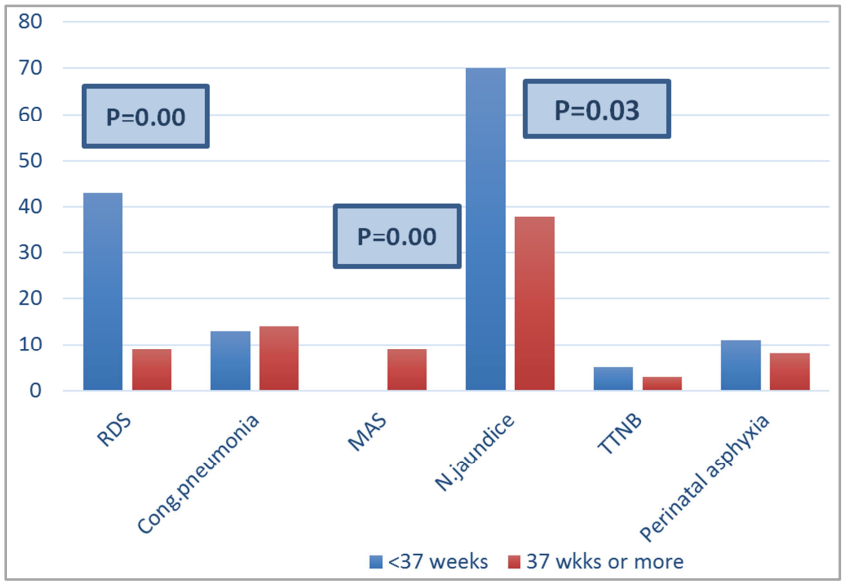

Figure 2. *Comparison of neonatal morbidities among PPHN cases in different gestation.*

The baseline RDW was compared between two groups and it showed that mean RDW was slightly higher among babies with PPHN and p value was significant (0.000) as shown in table 4. To find out the cut-off value of RDW, a ROC curve was drawn (Figure 3). The optimal RDW cut point for predicting PPHN was 17.05, which yielded sensitivity 84.7% and specificity 82.5%. Overall, the AUC of RDW was 0.917 (95% CI: 0.889 – 0.946, p < 0.001). Positive likelihood ratio and negative likelihood ratio were 4.84 and 0.19, respectively.

Table 4. *Comparison of baseline RDW among PPHN and Non-PPHN group.*

Variable	PPHN Group N=157	Non-PPHN Group N=160	P value
Mean RDW	17.82 ± 1.93	15.5 ± 1.1	0.000

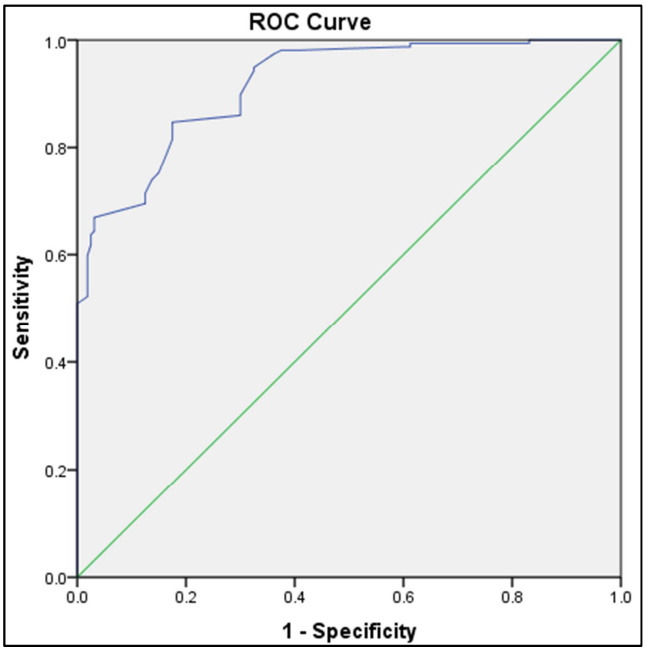

Figure 3. *Cut-off value of RDW in PPHN cases by using ROC.*

4. Discussion

PPHN is traditionally considered a disease of term and late preterm infants. Steurer MA et al. in their study found that late preterm infants are at highest risk of PPHN (5.4 per 1000 live births). It was due to higher rates of RDS and infection among this group [19]. Begum NA et al. also found PPHN more in late preterm [7]. Our study similarly observed cases with PPHN were mostly late preterm (p= 0.00).

In this study we found that male neonates developed PPHN more than female (66% vs 34%). This finding is similar with other studies [19]. However female sex is protective against respiratory distress syndrome (RDS) due to advanced fetal lung maturity. This might explain why males are more affected.

We observed the association of three maternal risk factors (HTN/PET, asthma, GDM) with PPHN. In multi-variate logistic regression, maternal hypertension/ pre-eclampsia and asthma were found significant risk factors for developing PPHN in newborns. Razzaq et al. Ahmed T and Begum NA also found that the offspring of women with hypertension during pregnancy experiences a higher- rates of PPHN [4, 6-7]. Maternal GDM was also found significant on univariate analysis and it is consistent with other study results [8].

Further analysis of neonatal morbidities among PPHN patients, showed in this study that, preterm PPHN (babies who were born at < 37 weeks) had RDS and jaundice more (p=0.00). On the other hand, term PPHN cases had meconium aspiration syndrome than pre-term neonates with PPHN (p=0.00). These findings are compatible with another studies [20, 21].

Although PPHN is commonly found in term and late preterm neonates, but evidence now increasingly suggests that, Preterm neonates with RDS present with pulmonary hypertension in early life whereas preterm infants with bronchopulmonary dysplasia (BPD) may present with PPHN later in hospital course or after discharge [20]. Similarly, Meconium aspiration syndrome (MAS) is the most common cause of PPHN and happens mostly in term and post term neonates. It causes partial or complete obstruction of the airway, thus decrease V/Q ratios and increase intrapulmonary right-to-left shunt which further leads to increased physiologic dead space and hypoxemia [21].

In this study, red cell distribution width was observed to identify its association with persistent pulmonary hypertension of newborn and found statistically significant. Mean RDW was higher among cases than controls (17.82 ± 1.93 vs 15.5 ± 1.1; p =0.000). Similar findings are observed in few adult studies where RDW was found higher in patients having pulmonary embolism, who were very sick and required mechanical ventilation [16, 18, 22]. This type of studies is limited in neonates. Moreover, some works have been done which revealed that RDW at day 28 of life could serve as a biomarker for predicting BPD and its severity but they have not seen PPHN [23].

Here the optimal cutoff value of RDW was 17.05 with a sensitivity of 85%. Overall, the AUC of RDW was 0.917 (p < 0.001). In another NICU based study done by Sagheb et al. also found similar findings (the optimal RDW cut point for prediction of PPHN by the ROC curve analysis was 17.9 with sensitivity = 85.71%) [24].

5. Conclusion

Red cell distribution width is found higher among PPHN cases with a cut off value of 17 (sensitivity of 85%). This RDW is a good bio marker to predict PPHN early in advanced NICU as well in resource poor setting. Further in-depth studies are needed to justify the current findings.

6. Recommendation

RDW can be a simple, valuable, accessible marker for predicting PPHN before performing echocardiography in hypoxemic NICU admitted neonates. This will avoid un-necessary delay in management.

Conflict of Interest

The authors declare that they have no competing interest.

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