Prevalence of pulmonary hypertension in preterm infants with Respiratory Distress

Abd El Mageed Mohammed Bayoumy[1] ,Mohammed Fawzy Fouad[1] ,Sherief abd aleal Mohamed[3]*

[1]Pediatric Department Faculty of Medicine - Al-Azhar University (Assiut)

[3]***Corresponding author:** Sherief Abd aleal Mohamed

Mobile:01001983380

E-mail:sherief3322@gmail.com

ABSTRACT

Background: Pulmonary Hypertension (PH) is increased pulmonary artery pressure which cause Precapillary PH, leading to high vascular resistance, right heart overload, and failure. **Aim:** To assess the prevalence of pulmonary hypertension in preterm infants with respiratory distress in NICU using Echo- cardiography.

Patients and methods: This was a prospective Study Conducted at Al-Azhar Assiut University, Pediatrics Department, NICU Unit, on 52 neonates with Respiratory Distress Syndrome(RDS) from June 1st , 2022, to December 31th , 2022.

Results: Our results showed that 36 cases (69.23%) had a small patent ductus arteriosus (PDA), while 9 cases (17.3%) had pulmonary hypertension and pulmonary stenosis. Normal cases accounted in 16 (30.77%). All patients received oxygen with continuous positive airway pressure (CPAP), with 75% requiring mechanical ventilation and endotracheal intubation. Additionally, 78.85% of the cases were treated with antibiotics (ampicillin and ceftazidime), while 21.15% received amikacin and meropenem. Dopamine and dobutamine were administered to 75% of the cases, and all patients received inhaled steroids. Sildenafil was given to 78.85%, and 88.46% received IV diuretics. Other treatments included correction of hypoglycemia and sodium bicarbonate infusion, which may contribute to improving respiratory and other conditions in these neonates.

Conclusion: PH was prevalent (17.3%) in preterm infants born at <35 weeks and presented with respiratory distress syndrome. So, Preterm birth, along with other factors, significantly contributes to the development of PH.

Key words: PH; PAH; PDA; CPAP.

INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic condition defined as an increase in mean pulmonary artery pressure (MPAP) In particular, PAH is characterized by the presence of precapillary PH due to relative blood flow obstruction proximal to the lung capillary bed and increased pulmonary vascular resistance (PVR). This results in right ventricular (RV) pressure overload, ultimately leading to right-heart failure and death. PAH can be idiopathic, heritable, drug or toxin induced, or associated with other medical conditions, such as congenital heart disease (CHD) and connective tissue disease.[1]

Persistent pulmonary hypertension puts the infant at risk for low blood oxygen levels, increased requirements for support, and long-term neuro- developmental impairment such as developmental delays, motor delays, and hearing loss.[2]

Transthoracic echocardiography is an excellent noninvasive screening test for patients with symptoms or risk factors for PH, by providing direct and/or indirect signs of elevated pulmonary artery pressure (PAP). It may also provide key information on both the etiology and the prognosis of PH Echocardiography is a pivotal screening test in symptomatic patients at risk for PAH. As an imaging modality, it has the advantage of being widely available, cost effective, and safe. It also plays an important role in assessing outcomes, monitoring the efficacy of specific therapeutic interventions for PH, and detecting the preclinical stages of disease. Newer ultrasound techniques may provide key additional information in the assessment of right-heart structure and function.[3]

Respiratory distress syndrome of the newborn, also called hyaline membrane disease, is the most common cause of respiratory distress in premature infants, correlating with structural and functional lung immaturity. It is most common in infants born at fewer than 28 weeks' gestation and affects one third of infants born at 28 to 34 weeks' gestation, but occurs in less than 5 percent of those born after 34 weeks' gestation. The condition is more common in boys, and the incidence is approximately six times higher in infants whose mothers have diabetes.[4]

The aim of this study was to assess the prevalence of pulmonary hypertension in preterm infants with respiratory distress in NICU using Echo- cardiography.

Ethical consideration:

1. Our study was approved by the ethical committee of Faculty of Medicine, Al-Azhar University, Assiut, and conducted in accordance with Helsinki standards 2013.
2. An informed consent was obtained from all parents and participating children.
3. The results and data of the study are confidential, and the patient has the right to keep it.
4. The authors received no financial support for the research, authorship, and/or publication of this article.
5. No conflict of interest regarding study or publications

Sample size calculations:

Sample size calculated based on the pilot study showing average of 59 pediatric Patients with respiratory distress, admitted to Alazhar Assiut university hospital pediatric department, NICU unit. With the allowable error of five percent (5%) and response distribution of 50%, a sample size for this study in patients have pulmonary hypertension over the study period of 6 months will be 52 (Raosoft sample size calculator).

Inclusion criteria: All preterm infants with gestational age (29weeks—34weeks) admitted to neonatal unit of, both sex, age: from 0 to 14 days and Evaluation for pulmonary hypertension with Echocardiography

Exclusion criteria: Major congenital anomalies, congenital heart disease except PDA and PFO of prematurity, birth weight less than 1000 gm and full-term infants.

Study procedure:

This was a prospective Study Conducted at Al-Azhar Assiut University, Pediatrics Department, NICU Unit, performed on 52 neonates from June 1, 2022, to December 31, 2022.

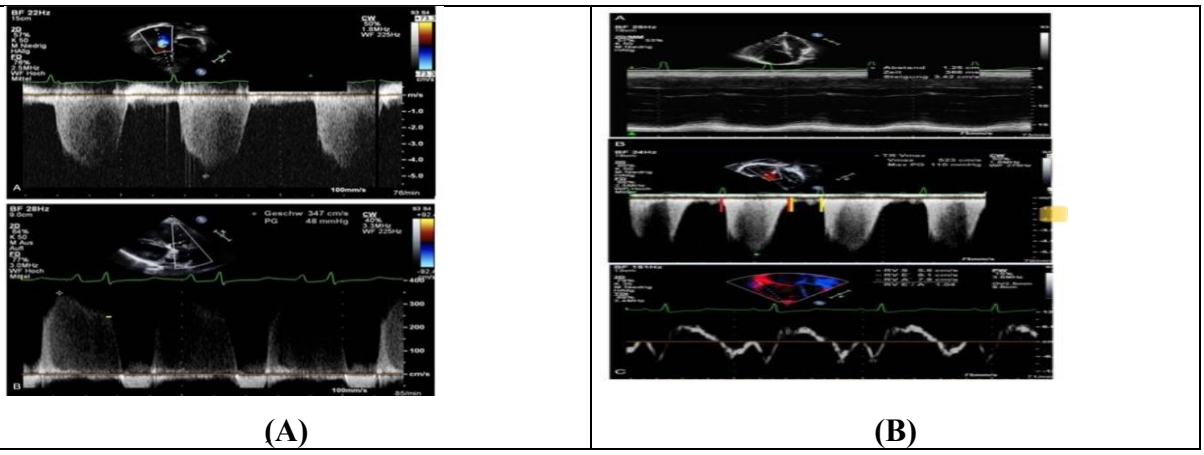
Effective diagnosis of chronic pulmonary hypertension (PH) relies on a comprehensive approach, including:

Detailed maternal history (last menstrual period, maternal diseases, and complications), birth history (gestational age, delivery type, and meconium aspiration syndrome), postnatal events (hypoxia and cyanosis), and family history (similar conditions or congenital heart defects in siblings).

A clinical examination for chronic pulmonary hypertension revealed signs of right ventricular failure, low oxygen saturation, cyanosis, and peripheral edema. Respiratory distress was also present. A comprehensive assessment included growth parameters, vital signs, and systemic examination of the gastrointestinal, respiratory, and neurological systems.

Echocardiographic assessment in pediatric pulmonary hypertension (PH) involved evaluating key parameters such as systolic pulmonary artery pressure (PAP), right ventricular (RV) function, RV strain, RV/LV diameter ratios, and pulmonary artery acceleration time (PAAT). Elevated RV pressure often caused septal flattening, resulting in a D-shaped left ventricle with reduced volumes but preserved systolic function. Left ventricular (LV) systolic function and Doppler measurements of valve inflow/outflow were also assessed.

The presence of pericardial effusion (PE) was considered a poor prognostic marker, though its impact on mortality in children remained unclear. Right atrium (RA) enlargement, indicating poor RV compliance or increased pressure, was also evaluated. Although echocardiographic findings alone were insufficient for a definitive PH diagnosis, they played a crucial role in guiding urgent treatment when cardiac catheterization was not feasible, especially in unstable patients.



(A) **(B)**

Figure (1): (A): Estimation of RV and PH pressure (B) Asses (TAPSE) in patient with pulmonary hypertension (PH).

Statistical analysis

Data were collected and analyzed using Microsoft Excel and imported into SPSS software (version 21.0). Qualitative data were presented as numbers and percentages, while quantitative data were expressed as mean ± standard deviation (SD). Statistical tests included the Chi-square test for associations between qualitative variables and the t-test for differences between quantitative independent groups. A p-value <0.05 was considered statistically significant, and <0.001 highly significant. Statistical parameters such as mean, SD, and t-statistics were computed to assess data variations and group differences.

RESULTS

Table (1): Demographic and prentatal history of included subjects

Parameter	Value (N = 52)
Maternal Age (Years)	28.31 ± 5.02
G .Age (weeks)	32.02 ± 1.18
Age of presentation (hours)	2.48 ± 1.65
Sex	
• Male	34 (65.38%)
• Female	18 (34.62%)
Residence	
• Rural	41 (78.85%)
• Urban	11 (21.15%)
Respiratory distress	3.02 ± 0.78
Delivery Method	
• Cesarean	45 (86.54%)
• Normal VD	7 (13.46%)

Table 1 summarizes the demographic and clinical characteristics of a study population of neonates with risk for respiratory distress.

Table (2): clinical characteristics of studied patients:

Parameter	Value (N = 52)
Rapid breathing	52 (100%)
Chest retractions	52 (100%)
Cold extremities	52 (100%)
poor suckling	52 (100%)
Nasal flaring	52 (100%)
Respiratory Grunting	37 (71.15%)
Tachycardia	39 (75%)
Central Cyanosis	41 (78.85%)

Table 2: describes the main clinical presentations of the study population
with 75% of patient s with tachycardia and 78.8% develop central cyanosis ,

Table (3): Echo findings of included subjects

Parameter	Value (N = 52)
Pulmonary HTN	36 (69.23%)
Small PDA , PFO	36 (69.23%)
PS	9 (17.3%)
Normal	16 (30.77%)

Table (4): correlation between Gestational age and pulmonary hypertension

Parameter	Value (N = 36)
GA (Weeks) (x ± S.D.)	33.78 ± 1.22
Week of Gestation	
32	1 (2.78%)
33	5 (13.89%)
34	8 (22.22%)
35	11 (30.56%)
36	9 (25%)
37	2 (5.56%)

This table shows the gestational age of 36 cases that presented with pulmonary hypertension. The mean gestational age was 34.78 weeks

Table (5): correlation between Gestational age of cases with grade of pulmonary hypertension

Parameter	Value (N = 36)	Grade of pulmonary hypertension
GA (Weeks)	33.78 ± 1.22	mild /moderate / severe
Week of Gestation		
32:33	6 (16.67%)	Severe (>70 mm hg)
34:36	28 (77.78%)	Moderate (50-70 mm hg)
37	2 (5.56%)	Mild (35-50 mm hg)

This table shows the gestational age of 36 cases that presented with respiratory distress and pulmonary hypertension. With PH grading

Table (6): Treatments of included subjects:

Parameter	Value (N = 52)
Oxygen Supply	52 (100%)
CPAP continuous positive airway pressure	52 (100%)
Mechanical ventilation	39 (75%)
Anti-biotics	
• Amikacin & Meropenem	11 (21.15%)
• Ampicillin & Ceftazidime	41 (78.85%)
Dopamine & dobutamine	39 (75%)
Inhaled steroids	52 (100%)
Sildenafil	41 (78.85%)
IV Diuretics	46 (88.46%)
• Correction of hypoglycemia, Alkalinization with sodium bicarbonate infusion	41 (78.85%)

Table table reports the treatments that were administered to the study population,

DISCUSSION

The current study aimed to assess the prevalence of pulmonary hypertension in newborn infants in NICU using Echocardiography In the present study we found that the majority was male neonates (65.38%) and a higher proportion of neonates from rural areas (78.85%). The mean maternal age is 28.31 years, and the mean gestational age of the neonates is 32.02 weeks. The neonates had an average grade of respiratory distress of 3.02 on a scale of 0-4, with 0 being no distress and 4 being severe distress.

Our results were supported by **Qari et al.**[5] who found that the greatest risk factor for respiratory distress syndrome is prematurity. Other risk factors of the disease are white male gender, diabetic mothers, cesarean section delivery, second born twins and infants with a family history of respiratory distress syndrome.

This correlated with the finding of the study of **Hernandez-Dias et al.**[6] who conducted a study on 377 infants with PHN and found that a male gender is a risk factor with increased number of affected males 239 (63.4%) when compared to number of affected females 138 (36.6%).

In this study we found that the majority of the neonates (86.54%) were delivered via cesarean section, while a small proportion (13.46%) were delivered via normal vaginal delivery.

This comes in agreement with **Araujo et al.**[7] who reported that cesarean section delivery was associated with a high incidence of respiratory distress syndrome and PHN.

In our study showed that, the main clinical presentations of the study population, which consists of 52 neonates with respiratory distress. All of the neonates

had rapid difficult breathing, cold extremities, poor suckling, chest retractions and nasal flaring. Respiratory grunting (71.15%), while a majority of the neonates (78.85%) had central cyanosis and tachycardia (75%). These clinical presentations may be indicative of various respiratory conditions in the neonates, such as respiratory distress syndrome, which may require medical intervention.

In this thesis we cleared that a proportion of the neonates 36 (69.23%) had a small patent ductus arteriosus (PDA), which is a congenital heart defect in which the ductus arteriosus, a blood vessel that normally closes after birth, remains open. Also, these 36 (69.23%) had pulmonary hypertension, which is a condition characterized by high blood pressure in the arteries of the lungs and, 9 neonates (17.3%) had a pulmonic stenosis, which is a narrowing of the pulmonic valve in the heart. Normal cases were 16 (30.77%) cases.
This was in accordance with **Dabour et al.**[8] who found a total number of neonates screened were 41, of which 18 (43.9%) cases had PH with presence of PDA.

In study to evaluate pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia, **Mourani et al.**[9] reported the overall incidence of PAH was 42%.

Arjaans et al.[10] found that the prevalence of PDA with a left- to-right shunt during the first 10 days of life in preterm infants born at<30 weeks of gestational age has been reported to be 65%-85% and is inversely related to gestational age.

Collaco et al.[11] also found that PH was 3 times more likely to be observed in infants with a history of patent ductus arteriosus requiring ligation in both the NICU population (OR: 3.19) and the BPD clinic population (OR: 2.67).

In this study we found that the mean gestational age was 32.78 weeks, with a standard deviation of 1.22 weeks. The majority of the cases (30.56%) were at 35 weeks of gestation, while the least number of cases (2.78%) were at 32 weeks of gestation. The distribution of cases across the different weeks of gestation is fairly evenly spread, with no single week comprising more than a quarter of the cases

Similarly, **Milas et al.**[12] found that 20% of admitted newborn in NICU have RD, 34% were preterm older than 32 weeks, and 12% of newborn were terms babies.

Arjaans et al.[10] found that the incidence of PH is high among preterm infants and increases with lower gestational age (up to 18% in infants born at 22 weeks).

Bhosgi et al.[13] found that when GA (weeks) with regards to PH was observed in cases group, the results suggested a high incidence of PH in term neonates 38% (18/47) as compared to preterm neonates 28.5% (14/49).

Magazine et al.[14] explained these variations due to different predisposing factors in each study and variations in health care facilities in various countries.

The incidence of RDS increases with decreasing gestational age, and infants born below 35 weeks gestation are at the greatest risk for RDS. In **Sakonidou and Dhaliwa,**[15] study, 4.4% of RDS cases were extreme preterm, the gestational age of their mothers ranged from 24 to 29 weeks, 86.5%were preterm babies with mother's gestational age ranged from 30-36 weeks while 4.4% and 4.7% of newborn were late preterm and full term respectively.

In this study we demonstrated that all of the subjects received oxygen supply and CPAP continuous positive air way pressure. A significant proportion of the subjects also received Mechanical ventilation (75%) and Endo tracheal intubation. The majority of the subjects (78.85%) received ampicillin and ceftazidime as anti-biotics, while a smaller number (21.15%) received amikacin and meropenem. Dopamine and dobutamine were given to 75% of the subjects, while inhaled steroids were given to all of the subjects. A significant proportion of the subjects (78.85%) also received Sildenafil, and almost all of the subjects (88.46%) required intravenous diuretics. Other treatments that were given to some of the subjects included correction of hypoglycemia, alkalinization with sodium bicarbonate infusion.

Bhosgi et al.[13] found that almost all neonates were on respiratory support and those initially who were on CPAP and HFNC, went in for mechanical ventilation 47 (94%).

CONCLUSION

In conclusion, PH was highly prevalent (69.23%) in a prospective cohort of preterm infants born at <35 weeks and presented with respiratory distress syndrome. So, Preterm birth, along with other factors, significantly contributes to the development of PH.

RECOMMENDATIONS

Further studies with larger sample size are needed to confirm the current results. Development of strategies aiming to reduction of RD among neonates through proper antenatal care to decrease the incidence of premature labor, evaluation of indication of cesarean section encourages hospital delivery. Furthermore, surveillance programs for neonatal mortality should include preventive measures and interventions for better natal care and postnatal care. Finally, improvement of health services quality in the NICU.

LIMITATION

Our study has few limitations, first because of retrospective nature, few essential data were lost. Second, is the small sample size of the study. On the other hand, strength of our study being that diagnosis of PH was confirmed in each and every case with echocardiography and was not solely based on clinical assessment.

References

Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, et al (**2012**). Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr. 2013 Jan. 10.1016/j.echo.2012.10.009.. PMID: 23140849.

Shivananda S, Ahliwahlia L, Kluckow M, Luc J, et al (2012) Variation in the management of persistent pulmonary hypertension of the newborn: a survey of physicians in Canada, Australia, and New Zealand. Am J Perinatol. 2012 Aug;29: 10.1055/s-0032-1310523. PMID: 22495900.

Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al (2018); American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation.. PMID: 29650544.

Melchior H, Kurch-Bek D, Mund M (**2017**). The Prevalence of Gestational Diabetes. Dtsch Arztebl Int.;114(24):412-418. PMID: 28669379; PMCID: PMC5499505.

QARI, Shahad Abdulhafith, et al (**2018**). Prevalence of respiratory distress syndrome in neonates. The Egyptian journal of hospital medicine, 10.12816/0043086

Hernández-Díaz S, Van Marter LJ, Werler MM, Louik C,(2007). Risk factors for persistent pulmonary hypertension of the newborn. Pediatrics.;120(2):e272-82. doi: 10.1542/peds.2006-3037. PMID: 17671038.

Araujo OR, Albertoni Ade C, Lopes VA, Louzada ME, Lopes AO, Cabral EA, et al(**2008**). Cesarean deliveries and other risks for persistent pulmonary hypertension of the newborn. Rev Bras Ter Intensiva.;20(4):394-7. English, Portuguese. PMID: 25307245.

DABOUR, S. A., et al. (**2015**) Risk Factors and Outcomes of Early Pulmonary Hypertension in Preterm Neonate. Benha Journal of Applied Sciences, 2021, 10.21608/bjas.2021.169164

Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al.(**2018**) Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am J Respir Crit Care Med.. PMID: 25389562; PMCID: PMC4299632.

Arjaans S, Fries MWF, Schoots MH, Schilte CFM, Roofthooft MTR, Vrijlandt EJLE, et al(**2022**). Clinical Significance of Early Pulmonary Hypertension in Preterm Infants. J Pediatr. 2022 Aug 4. PMID: 35934129.

Collaco JM, Dadlani GH, Nies MK, Leshko J, Everett AD, McGrath-Morrow SA (**2016**). Risk Factors and Clinical Outcomes in Preterm Infants with Pulmonary Hypertension. PLoS One. PMID: 27716811; PMCID: PMC5055317.

MILAS, KREŠIMIR, et al (**2017**). Causes of respiratory distress among neonates of gestational age 32 weeks and more. Signa Vitae,:10.1007/s00431-023-05238-z.

Bhosgi R, Kumar N, Kadegaon B, Soumya DKA.(**2020**). Retrospective study on profile of persistent pulmonary hypertension of newborn in neonates admitted to sick newborn care unit

Rao S, Chogtu B, Venkateswaran R, Shahul HA, Goneppanavar , et al (**2017**). Epidemiological profile of acute respiratory distress syndrome .10.4103/0970-2113.197097. PMID: 28144059; PMCID: PMC5234197.

Sakonidou S, Dhaliwal J(**2015**). The management of neonatal respiratory distress syndrome in preterm infants (European Consensus Guidelines--2013 update). Arch Dis Child Educ Pract. 2015 Feb 18. PMID: 25694422.