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Frequency and Risk Factors Associated with Retinopathy of Prematurity: A Single Centre Study

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ABSTRACT

Retinopathy of prematurity is the irregular development of blood vessels in the growing retina of premature infants, which can primarily lead to blindness. **Objective:** To identify frequency and risk factors associated with retinopathy of prematurity. **Methods:** A cross-sectional study was conducted on 140 premature infants (gestational age ≤34 weeks) investigated in the Neonatal Intensive Care Unit of Central Park Teaching Hospital, Lahore. Preterm neonates' weight ≤1.8 Kg and gestational age ≤34 weeks were enrolled. The neonate's demographic details, risk factors for retinopathy, eye examinations, and follow-up were recorded. Their maternal history included maternal age, gestational age, and maternal risk factors. During their hospital stay, clinical progress, morbidity, and mortality were assessed and monitored. Descriptive statistics were done using SPSS version 26.0. **Results:** From these 140 premature infants, 74 (52.9%) were male and 66 (47.1%) were female. The average gestational age was 30.4 ± 2.36 weeks, with a mean birth weight of 1.3 ± 0.28 kg. Of total premature infants, 14 (10%) developed Retinopathy of premature whereas 6 (4.3%) infants expired and 21 (15%) lost to follow-up. Grade-I and Grade-II retinopathy of prematurity were developed in 8 (57.1%) and 6 (42.9%), respectively and based on regression analysis, low gestational age, respiratory distress syndrome, and sepsis independently predicted the onset of prematurity. **Conclusions:** It was concluded that the prevalence of retinopathy of prematurity was 10%. Lower gestational age, blood transfusion, lower birth weight, anemia, bronchopulmonary dysplasia, sepsis, and O2 therapy were primary factors of risk in retinopathy of prematurity development.

INTRODUCTION

Retinopathy of prematurity (ROP) is the abnormal growth of retinal blood vessels, caused by defective retinal vascularity which in turn is caused by hyperoxia that results in vascular endothelial growth factor (VEGF) and endothelial cell regulation and death [1]. In developing countries, blindness and visual impairment are mostly caused by retinopathy of prematurity, which is a major contributor [2]. The increasing incidence of Retinopathy of prematurity (ROP) is mainly dependent on the improvement required in the increasing survival from the low birth weight and preterm cases, by improving the neonatal services in the developing countries. The gestational age, gender, birth weight, and the standard of neonatal care are the several factors that affect the incidence of Retinopathy of prematurity (ROP) [3-5]. Many investigations identified different risk factors related to the Retinopathy of prematurity (ROP) with potential causes leading to mortality. These risk factors consist of premature gestational age, excessive mechanical ventilation, low birth weight (LBW), Anemia, Apgar score, Intraventricular hemorrhage (IVH), exposure to supplementary oxygen (O2), and septicemia [6]. Sepsis, metabolites, blood transfusion, gender, and mechanical ventilation or other risk factors are the potential causes of ROP. The condition involves abnormal retinal blood vessel growth in premature infants, leading to fragile vessels that can leak or bleed. This can be a cause of retinal scarring and tractional detachment, the major source of visual impairment and loss of sight in Retinopathy of prematurity (ROP), highlighting the need for early detection and intervention [7]. In preterm Births,

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Pakistan ranks as the 4th country, with rural areas facing low survival rates due to the limited healthcare available. Urban improvements in Neonatal Intensive Care Units (NICUs) have increased survival rates but also increased Retinopathy of prematurity (ROP) cases, which are a major cause of childhood blindness. Retinopathy of prematurity (ROP) often goes under-recognized in Pakistan due to the high rates of low birth weight (LBW) and preterm births, lack of availability of standardized protocols, insufficient awareness among the family physicians, and substandard neonatal care [8, 9]. The frequency of ROP in Pakistan varies from 10.5% to 24.6% [10, 11]. The high preterm birth rate in Pakistan and healthcare disparities create important challenges in managing Retinopathy of prematurity (ROP). While improvements in urban neonatal care have increased cases of Retinopathy of prematurity (ROP), the rural areas still struggle with low survival rates. ROP is often under-recognized due to the high rate of low birth weight, lack of availability of standardized protocols, and limited awareness of providers.

This study aims to measure the frequency and risk factors of Retinopathy of prematurity (ROP) in premature infants, improve awareness among the pediatricians, and implementation of effective management strategies.

METHODS

A cross-sectional study was conducted on 140 premature infants (gestational age ≤34 weeks) investigated in the NICU of Central Park Teaching Hospital, Lahore from October 2021 to September 2022. This article is acknowledged by the approval of the Institutions' Ethical Committee and IRB No. is CPMC/IRB-No/1462. All preterm neonates weight ≤1.8 Kg and GA ≤34 weeks were enrolled and consent was acquired from their parents during the interview process. All patients with congenital malformation, tumor of the eye congenital cataract, incomplete screening procedure, oxygen not required, and death before initial screening were excluded. 95% Confidence Interval and 5% margin of error as per the WHO Sample size calculator was to determine the 140 patients by keeping a prevalence of 10.5% [10]. Data regarding risk factors and development of perinatal and neonatal conditions in the hospital were obtained from the medical records of the infants. Where ROP was not diagnosed, eye examinations were performed every two weeks until the retina returned to normal neuropathy. For infants with ROP, frequency was determined by the severity of the condition. Ophthalmoscopy was performed in three consecutive guides spaced 15 minutes apart after application of tropicamide 0.5% and phenylephrine 2.5% eye drops. Binocular indirect ophthalmoscopy was performed with a 20 D lens, the procedure included a standard lid speculum and scleral depressor. The neonate's demographic details, risk factors for retinopathy, eye examinations, and follow-up were recorded. Maternal history of neonates included maternal age, gestational age, and maternal risk factors. During their hospital stay, the clinical progress, morbidity, and mortality were assessed and monitored. Descriptive statistics were conducted using SPSS version 26.0. Quantitative variables were presented as means and standard deviations, while qualitative variables were expressed as frequencies and percentages. Fisher's exact test or T-test was employed to assess the association between risk factors such as hyaline membrane disease, surfactant administration, transient tachypnea of the newborn (TTN), phototherapy, patent ductus arteriosus, sepsis, hemorrhage, anemia, and blood transfusion and ROP, with a 95% confidence interval and a 5% significance level.

RESULTS

Among the 140 premature infants, 74 (52.9%) were male and 66 (47.1%) were female. The mean gestational age was 30.4 ± 2.36 weeks, and the mean birth weight was 1.3 ± 0.28 kg. Of the total premature infants, 14 (10%) developed Retinopathy of premature whereas 6 (4.3%) infants expired and 21 (15%) lost to follow-up. Grade-I and grade-II ROP were developed in 8 (57.1%) and 6 (42.9%), respectively. The clinical parameters of patients are described in table 1.

Table 1: Clinical Parameters of Patients (n=140)

Clinical Parameters	Total n (%)
Gestational Age (Weeks)	
<30	26 (18.6%)
30-32	30 (21.4%)
32-34	84 (60%)
Birth Weight (Kg)	
<1	19 (13.6%)
1-1.2	22 (15.7%)
1.3-1.5	21 (15%)
1.6-1.8	78 (55.7%)
Anemia	
Hb <13.0 mg/dl	14 (10%)
Hb >13.0 mg/dl	126 (90%)
Sepsis	
Yes	48 (34.2%)
No	92 (65.8%)
Breastfeeding	
Yes	20 (14.3%)
No	120 (86.7%)
Types of Delivery	
Cesarean	101 (72.1%)
Normal Vaginal Delivery (NVD)	39 (27.9%)
Oxygen Therapy	
Yes	108 (77.1%)
No	32 (22.9%)
Mechanical Ventilation	
Yes	49 (35%)
No	91 (65%)

Respiratory distress syndrome (RDS)	
Yes	64 (45.7%)
No	76 (54.3%)
Transient Tachypnea of the Newborn	
Yes	27 (19.3%)
No	113 (80.7%)
Borderline Personality Disorder	
Yes	9 (6.4%)
No	131 (93.6%)
Necrotizing Enter Colitis	
Yes	6 (4.3%)
No	134 (95.7%)
Ductus Arteriosus Persistence	
Yes	19 (13.6%)
No	121 (76.4%)
Intraventricular Hemorrhage	
Yes	5 (3.6%)
No	135 (96.4%)

The occurrence rate of patients with ROP as per their birth weight was as follows: 3 (21.4%) <1 kg, 8 (57.1%) in 1-1.2 kg, 2 (14.3%) in 1.3-1.5 kg, and 1 (7.1%) in 1.6-1.8 kg. Based on the gestational age, patients with ROP were as follows: 9 (64.3%) in <30, 3 (21.4%) in 30-32, and 2 (14.3%) in 32-34 weeks Comparison of risk factors through univariate analysis are shown in table 2.

Table 2: Comparison of Risk Factors Through Univariate Analysis

Risk Factors	Positive (n=14)	Negative (n=91)	OR 95%CI
Gestational Age (Weeks)	29.4 ± 1.8	31.4 ± 2.92	–
Birth Weight (Kg)	1.4 ± 0.34	1.2 ± 0.22	–
Duration of O_2 Supplement (Days)	18.9 + 11.6	3.6 + 2.9	–
Mechanical Ventilation (Days)	17.8 + 11.1	4.7 + 2.5	–
Number of Blood Transfusion	16.4 + 10.3	6.1 + 3.9	–
Gender N (%)			
Male	6 (42.9%)	45 (49.5%)	1.2 (0.3-3.2)
Female	8 (57.1%)	46 (50.5%)	
Sepsis			
Yes	10 (71.4%)	38 (41.8%)	7.3 (2.3-22.9)
No	4 (28.6%)	53 (58.2%)	
RDS			
Yes	13 (92.9%)	49 (53.8%)	9.1 (2.3-21.9)
No	1 (7.1%)	42 (46.2%)	
Surfactant Therapy			
Yes	9 (64.3%)	58 (63.7%)	2.7 (0.9-7.9)
No	5 (65.7%)	33 (32.3%)	
Anemia			
Yes	12 (85.7%)	60 (65.9%)	2.3 (0.6-8.2)
No	2 (14.3%)	31 (34.1%)	
Intraventricular Hemorrhage			
Yes	4 (28.6%)	1 (1.1%)	12.8 (1.2-119.1)
No	2 (14.3%)	90 (98.9%)	

Based on regression analysis, low gestational age, respiratory distress syndrome, and sepsis independently predicted the onset of ROP in table 3.

Table 3: Several Logistic Regression Analyses Were Executed for the Independent Predictors Identifications Involved in ROP Development

Risk Factors	Adj. OR (95% CI)	p-Value
Gestational Age (Weeks)	0.5 (0.3-0.9)	0.5
Sepsis	10.9 (2.3-48.7)	0.001
RDS	13.8 (1.6-114.6)	0.011

DISCUSSION

The present study mainly focused on the prevalence and risk factors associated with premature of retinopathy and found that the incidence of POR was 10% among 140 premature infants. Preterm delivery, blood transfusion, low birth weight, anemia, pulmonary embolism, sepsis, and oxygen therapy emerged as ROP major risk factors. The incidence of ROP varies from 13.2% to 46% in developed countries [12, 13]. Retinopathy of prematurity (ROP) is the principal root cause of childhood blindness all over the world, underscoring the critical requirement for well-established newborn intensive care units and upgraded survival rates for premature infants. The prevalence of ROP varies notably across different demographic and ethnic groups, reflecting disparities in healthcare access and neonatal care practices. In India, the incidence of ROP varies from 38% to 47%, highlighting the significant burden of the condition in the country. This high prevalence is often associated with the challenges faced in newborn care, including the management of preterm infants and the availability of specialized medical resources. In Thailand, ROP prevalence varies between 14% and 33%, indicating a somewhat lower but still considerable impact. This variability can be influenced by differences in healthcare infrastructure, screening programs, and treatment practices across regions. In Mexico, ROP accounts for 24% of childhood blindness cases, illustrating its significant role in visual impairment among children. This prevalence reflects ongoing challenges in addressing ROP despite advances in newborn care [14]. The incidence of ROP varies across countries amongst newborns with a gestational age of <30 to 34 weeks and a birth weight ranging from 1,000 to 2,500 grams. In this study, 44.7% of neonates showed improvement in ROP indicating a positive response to management or therapy, while 32.7% showed no improvement. The research also highlighted variations in risk factors affecting ROP development and progression, with LBW and LGA identified as significant risk factors. These factors increase the vulnerability of the retina in premature neonates, contributing to the irregular blood vessel growth characteristic of ROP, which can lead to severe complications if not properly addressed [15]. In the current study, the mean GA and birth weight was 30.4 ± 2.36 weeks and 1.3 ± 0.28 kg, respectively, which was significantly lower than infants without ROP. GA in ROP diagnosis in infants with ROP progression and weight is

surprisingly low. However, no significant association was found between GA thickness at peak ROP stage and risk of ROP. Studies have consistently shown these factors to be highly correlated with ROP [16]. Specifically, premature infants with pulmonary hemorrhage and sepsis were found 15 times more likely to grow ROP, making these variables the most prominent risk factors. Early onset of the infection plays a significant part in the growth of ROP, often resulting from intrauterine or dormant infections during delivery. The incidence of infection rises as birth weight decreases, while mortality rates inversely correlate with gestational age [17]. The proposed strong association between neonatal respiratory infections and the development of ROP. Resting infants require increased mechanical ventilation (MV) and oxygen supplementation, which may increase the risk of ROP. Both pulmonary hypertension and Respiratory distress syndrome (RDS) are linked with ROP. RDS is due to surfactant deficiency and usually requires MV oxygen therapy, making neonates with RDS more susceptible to ROP. Most infants with RDS take surfactant therapy, and few researchers have proposed a strong association between surfactant therapy and ROP [18, 19]. This suggests that the potential risk of ROP may be increased in infants with RDS who require such treatment. Multiple regression analysis has identified sepsis, low gestational age, and respiratory distress as three key influencing factors for the growth of ROP. Amongst these, abnormal growth consistently stands out as the utmost important independent predictor for ROP growth [20]. Furthermore, symptoms of respiratory distress have been shown to predict the development of ROP by themselves [21]. This study is limited to certain factors. The study was performed in one tertiary care hospital, which means that the samples were only selected from a limited geographical area. Therefore, the findings of the study may not apply to the entire region or the whole country.

CONCLUSIONS

It was concluded that a significant number of premature newborns developed retinopathy of prematurity (ROP) due to a combination of factors, including lower gestational age, lower birth weight, sepsis, oxygen therapy, paler, and blood transfusion. ROP is an important and avoidable reason for childhood blindness in our populations.

Authors Contribution

Conceptualization: MZ
Methodology: MZ, AR[1], IY
Formal analysis: AA, WQ, AR[1], AR[2], IY
Writing review and editing: MZ, AA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

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