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A Study to Determine the Role of Septicemia in Retinopathy of Prematurity Among Preterm Babies

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Abstract: ***Background: Retinopathy of prematurity (ROP) is a major cause of preventable childhood blindness among preterm infants worldwide. The immature retinal vasculature in premature neonates is highly susceptible to various perinatal risk factors, including low birth weight, prematurity, oxygen therapy, and systemic infections such as septicemia. Neonatal sepsis can trigger inflammatory responses that interfere with normal retinal vascular development, thereby increasing the risk of development and progression of ROP. Objectives: The objectives of the present study were to determine the role of septicemia in the development of retinopathy of prematurity among preterm babies and to analyze low birth weight (<2 kg) as a significant risk factor associated with the occurrence of retinopathy of prematurity. Methods: This prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU), Department of Pediatrics, Saraswathi Institute of Medical Sciences, Hapur, over a period of two years. A total of 80 preterm neonates with gestational age less than 34 weeks and birth weight less than 2 kg were included using a convenience sampling method. Detailed maternal and neonatal information was recorded using a structured proforma. Screening for ROP was performed by an ophthalmologist using indirect ophthalmoscopy at recommended intervals. Data were analyzed using Microsoft Excel and SPSS software. Statistical analysis included descriptive statistics and Chi-square test to evaluate the association between septicemia, low birth weight and the occurrence of ROP. Results: Among the 80 preterm neonates included in the study, a considerable proportion developed retinopathy of prematurity. The incidence of ROP was significantly higher among neonates with septicemia compared to those without infection. Lower birth weight and decreased gestational age were also found to be strongly associated with the development of ROP. Additionally, factors such as prolonged oxygen supplementation and blood transfusion showed an increased association with ROP in preterm infants. Conclusion: Septicemia is an important risk factor contributing to the development of retinopathy of prematurity among preterm neonates. Low birth weight and prematurity further increase the susceptibility to ROP. Early detection, effective infection control, and regular ROP screening in neonatal intensive care units are essential to prevent severe visual impairment in premature infants.***

Keywords: Retinopathy of prematurity, Neonatal septicemia, Preterm infants, Low birth weight, Neonatal intensive care unit, ROP screening

1. Introduction

Retinopathy of prematurity (ROP) remains a significant cause of visual morbidity in preterm infants globally. The pathogenesis of ROP is closely intertwined with the developmental vulnerability of the immature retinal vasculature, which is impacted by various perinatal factors encountered by preterm neonates.

Among these, systemic infections like septicemia have emerged as important contributors due to their potential to exacerbate retinal injury through inflammatory and vascular pathways.[1]

For preterm babies, the risk of developing ROP is influenced by both intrinsic factors, like low gestational age and birth weight and extrinsic factors, including exposure to hyperoxia and serious infections, notably sepsis. Sepsis in neonates triggers a systemic inflammatory response, releasing cytokines and other mediators that can disrupt normal retinal vascular development.

Recent clinical and epidemiological evidence supports a strong association between episodes of neonatal sepsis and an elevated risk for both onset and progression of ROP, with recurrent sepsis episodes further increasing the odds of severe disease.[2]

The mechanisms by which septicemia contributes to ROP are multifactorial and may include direct vascular endothelial injury, increased vascular permeability and formation of microthrombi in retinal vessels, all of which are aggravated by the immature immune responses of preterm infants.

Studies have showed that not only is sepsis linked with the initial stages of ROP, but it also promotes severe forms requiring intervention. As such, understanding the role of neonatal sepsis is critical, both for risk stratification and preventive strategies in the management of ROP among premature babies.[3]

Recent large-scale cohort studies, like one from the German Neonatal Network and the Norwegian Neonatal Network, have reinforced these findings, concluding that culture-proven recurrent sepsis episodes are a preventable risk factor in the development and clinical course of ROP among infants born at less than 29 weeks of gestation. [4] The growing body of evidence underlines the importance of rigorous infection control and timely management of sepsis in neonatal intensive care units as a fundamental component of ROP prevention.

With this background present study is done to determine the role of septicemia in retinopathy of prematurity (ROP) among preterm babies.

2. Methodology

Study Area: The study was conducted on preterm neonates both inborn and outborn with Period of gestation (POG) < 34 weeks and weight < 2 kgs in the Neonatal-ICU, Department of Pediatrics Saraswathi Institute of Medical Sciences, Hapur.

Study Design: The study was designed as a prospective observational study.

Study Period: The study was carried out over a period of 24 months

Sample Size: The final sample size included 80 neonates.

Calculation of Sample Size:
Sample size for study were calculated by using formula as below:

$$n = \frac{z^2pq}{E^2}$$

where,
n = sample size
p = prevalence (considered from previous study is 27.9%)
q = 100 – p , So q = 72.1
E = error 10%
z = 1.96 (at 95% confidence interval)
So,

$$n = \frac{(1.96)^2 \times 27.9 \times 72.1}{0.10 \times 0.10}$$

Hence, the sample size is 80.

3. Results

A total of 80 preterm neonates were included in the study. Gender distribution was nearly equal, with 39 (48.8%) males and 41 (51.2%) females. The mean gestational age at birth was 31.0 weeks. Most neonates were born between 28–30 weeks of gestation (41.3%), followed by 33–34 weeks (32.5%) and 31–32 weeks (26.3%). The mean birth weight was 1.57 kg. A majority of infants (66.3%) had a birth weight between 1.5–2.0 kg, while 23.8% weighed between 1.0–1.5 kg and 10.0% had a birth weight below 1.0 kg.

Table 1: Baseline demographic and neonatal characteristics (N = 80)

Variable	Category	n (%) / Mean ± SD
Gender	Male	39 (48.8)
	Female	41 (51.2)
Gestational age at birth (weeks)	31.0 ± 1.7	
Gestational age group (weeks)	28–30	33 (41.3)
	31–32	21 (26.3)
	33–34	26 (32.5)
Birth weight (kg)	1.57 ± 0.35	
Birth weight group (kg)	<1.0	8 (10.0)
	1–1.5	19 (23.8)
	1.5-2.0	53 (66.3)

Retinopathy of prematurity was observed in 24 (30.0%) of the preterm neonates, while 56 (70.0%) did not develop ROP. Among the study population, 56 (70.0%) infants had no evidence of ROP. Of those diagnosed with ROP, the most common stage was Stage 1, seen in 9 (11.3%) neonates, followed by Stage 3 in 8 (10.0%) and Stage 2 in 7 (8.8%). These findings show that nearly one-third of the preterm infants developed ROP, with a notable proportion progressing to higher stages.

Table 2 : Incidence and staging of retinopathy of prematurity (ROP)

Variable	Category	n (%)
ROP	Present	24 (30.0)
	Absent	56 (70.0)
ROP stage	None	56 (70.0)
	Stage 1	9 (11.3)
	Stage 2	7 (8.8)
	Stage 3	8 (10.0)

ROP was more frequently observed among female neonates (62.5%) compared to males (37.5%); however, this difference was not statistically significant (p = 0.188). A higher proportion of ROP cases were noted in infants born at 28–30 weeks of gestation (58.3%), though gestational age group did not show a significant association with ROP (p = 0.121). Birth weight showed a strong and statistically significant association with ROP, with a higher incidence seen in neonates weighing less than 1.5 kg compared to those weighing ≥1.5 kg (p < 0.001)

Table 3 : Association of gender, gestational age, birth weight with ROP

Variable	Category	ROP Present n (%)	ROP Absent n (%)	p value
Gender	Male	9 (37.5)	30 (53.6)	0.188
	Female	15 (62.5)	26 (46.4)	
Gestational age group (weeks)	28–30	14 (58.3)	19 (33.9)	0.121
	31–32	4 (16.7)	17 (30.4)	
	33–34	6 (25.0)	20 (35.7)	
Birth weight group (kg)	<1.0	5 (20.8)	3 (5.4)	<0.001
	1.001–1.5	11 (45.8)	8 (14.3)	
	≥1.5	8 (33.3)	45 (80.4)	

Septicemia was significantly associated with ROP, as 79.2% of infants with ROP had documented sepsis compared to 51.8% in the non-ROP group (p = 0.022).

Table 4: Association of sepsis with ROP

Septicemia	ROP Present n (%)	ROP Absent n (%)	p value
Present	19 (79.2)	29 (51.8)	0.022
Absent	5 (20.8)	27 (48.2)	

Significant association was observed between ROP and anemia (p = 0.607) or mode of delivery (p = 0.921).

Table 5: Association of anemia, with ROP

Anemia	ROP Present n (%)	ROP Absent n (%)	p value
Present	5 (20.8)	9 (16.1)	0.607
Absent	19 (79.2)	47 (83.9)	

A history of blood transfusion was significantly more common among infants with ROP (75.0%) than those without ROP (37.5%) (p = 0.002).

Table 6 : Association of Blood transfusion with ROP

Blood transfusion	ROP Present n (%)	ROP Absent n (%)	p value
Present	18 (75.0)	21 (37.5)	0.002
Absnet	6 (25)	35 (62.5)	

There was no significant association observed between ROP and mode of delivery (p = 0.921)

Table 7: Association of mode of delivery with ROP

Mode of delivery	ROP Present n (%)	ROP Absent n (%)	p value
Normal	10 (41.7)	24 (42.9)	0.921
LSCS	14 (58.3)	32 (57.1)	

The mean duration of oxygen supplementation was higher among neonates who developed ROP compared to those who did not (4.00 days vs 2.21 days). This difference was statistically significant (p = 0.010), showing that prolonged oxygen exposure was significantly associated with the development of retinopathy of prematurity in the study population.

Table 8: Duration of oxygen supplementation and ROP

Variable	ROP Present (Mean ± SD)	ROP Absent (Mean ± SD)	p Value
Duration of oxygen supplementation (days)	4.00 ± 3.20	2.21 ± 2.56	0.010

The duration of oxygen supplementation showed a progressive increase with advancing stages of ROP. Neonates without ROP had a mean oxygen supplementation duration of 2.21 days, which was comparable to those with Stage 1 ROP (2.22 days). However, a marked increase was observed in infants with Stage 2 ROP (3.43 days) and the highest duration was noted among those with Stage 3 ROP (6.50 days). This trend was statistically significant on ANOVA analysis (p < 0.001), showing a strong association between prolonged oxygen exposure and increasing severity of retinopathy of prematurity.

Table 9: Duration of oxygen supplementation according to ROP stage

ROP Stage	Mean ± SD (days)
None	2.21 ± 2.56
Stage 1	2.22 ± 2.95
Stage 2	3.43 ± 2.94
Stage 3	6.50 ± 2.20
p value (ANOVA)	<0.001

Neonates who developed ROP had a significantly lower mean gestational age at birth compared to those without ROP (30.38 weeks vs 31.30 weeks; p = 0.027). Similarly, the mean birth weight was significantly lower in the ROP group than in the non-ROP group (1.25 kg vs 1.71 kg; p < 0.001). These findings show that lower gestational age and lower birth weight are significant risk factors for the development of retinopathy of prematurity.

Table 10 : Gestational age and birth weight in relation to ROP

Variable	ROP Present (Mean ± SD)	ROP Absent (Mean ± SD)	p value
Gestational age (weeks)	30.38 ± 1.86	31.30 ± 1.61	0.027
Birth weight (kg)	1.25 ± 0.29	1.71 ± 0.28	<0.001

Gestational age and birth weight varied significantly across different stages of ROP. The mean gestational age was highest among infants without ROP (31.30 weeks) and lowest in those with Stage 1 ROP (29.67 weeks), with a statistically significant difference across stages (p = 0.045). Birth weight showed a more pronounced and consistent decline with increasing ROP severity. Infants without ROP had the highest mean birth weight (1.71 kg), whereas those with Stage 3 ROP had the lowest mean birth weight (1.16 kg). The association between decreasing birth weight and increasing ROP stage was highly significant (p < 0.001).

Table 11: Gestational age and birth weight according to ROP stage

ROP Stage	Gestational age (weeks) Mean ± SD	Birth weight (kg) Mean ± SD
None	31.30 ± 1.61	1.71 ± 0.28
Stage 1	29.67 ± 1.80	1.35 ± 0.35
Stage 2	30.43 ± 2.07	1.21 ± 0.27
Stage 3	31.13 ± 1.64	1.16 ± 0.22
p value (ANOVA)	0.045	<0.001

Correlation analysis showed a strong negative correlation between birth weight and ROP stage (r = −0.598, p < 0.001), showing that lower birth weight was associated with more advanced stages of ROP.

Table 12: Correlation of ROP stage with Birth weight

Variable	Pearson correlation (r)	p value
Birth weight (gm)	−0.598	<0.001

The duration of oxygen supplementation showed a moderate positive correlation with ROP stage (r = 0.412, p < 0.001), showing that longer exposure to supplemental oxygen was associated with increasing severity of retinopathy of prematurity.

Table 13: Correlation of ROP stage with Duration of oxygen supplementation

Variable	Pearson correlation (r)	p value
Duration of oxygen supplementation	0.412	<0.001

4. Discussion

Incidence of Retinopathy of Prematurity

In the present study, Retinopathy of Prematurity (ROP) was observed in 24 out of 80 preterm neonates, giving an overall incidence of 30.0%. This finding falls well within the range reported in existing literature, where ROP incidence among screened high-risk preterm infants typically varies between 20% and 40%. A tertiary care center-based study involving 352 preterm infants (gestational age ≤32 weeks or birth weight ≤1500 g) reported a higher ROP incidence of 40.9%, although only 4.8% required treatment. In contrast, epidemiological data from the United States reported by Bhatnagar et al. [61] showed lower overall ROP incidence rates, increasing from 4.4% in 2003 to 8.1% in 2019, showing differences in population characteristics, screening criteria and neonatal care practices. The comparatively moderate incidence observed in our cohort may be attributable to the majority of infants with gestational age above 28 weeks and birth weight ≥1.5 kg.

Staging Pattern of Retinopathy of Prematurity

With respect to disease severity, the majority of infants in our study either had no ROP (70.0%) or milder forms of the disease, with Stage 1 observed in 11.3% and Stage 2 in 8.8% of neonates. Stage 3 ROP was identified in 10.0% of cases. This staging distribution is broadly consistent with previous studies showing a majority of early-stage ROP. Kumar et al.[62], in a prospective study of 63 infants with ROP, reported Stage 1 in 30%, Stage 2 in 63.5% and Stage 3 in 9.5% of cases, with most disease localized to Zone II. Similarly, an Indian study screening 200 preterm neonates reported an overall ROP incidence of 27.5%, with Stage 1 accounting for 65.5%, Stage 2 for 30.9% and Stage 3 for only 3.6% of cases. Compared to these reports, our study shows a slightly higher proportion of Stage 3 disease, which may show referral bias or delayed presentation in a tertiary care setting.

Association of Gender with Retinopathy of Prematurity

In the present study, females constituted a slightly higher proportion of the cohort (51.2%) compared to males (48.8%). This near-equal gender distribution is broadly consistent with existing literature, although many studies have reported a mild male majority among preterm infants, particularly those developing retinopathy of prematurity (ROP). A Turkish study involving 458 preterm neonates reported that males constituted 55.8% of infants with ROP compared to 52.3% among non-ROP infants, showing a male majority, although the difference was not statistically significant ($p > 0.05$). Similarly, Wang et al. [63], in a Chinese twin study of 112 preterm infants, observed no significant gender difference in ROP incidence, with rates of 21.42% in smaller twins and 16.07% in larger twins. The findings of the present study are similar to these reports, showing that while male sex is frequently observed among preterm cohorts, gender alone may not be a decisive determinant of neonatal outcomes.

In the present study, female neonates constituted a higher proportion of ROP cases (62.5%) compared to males (37.5%); however, this difference was not statistically significant ($p = 0.188$). This finding is similar to several studies showing that gender does not consistently influence the occurrence of any-stage ROP. Nevertheless, evidence from large meta-analyses shows a male disadvantage in severe ROP. Hundscheid et al. [64], in a comprehensive meta-analysis, reported higher odds of severe, treatment-requiring ROP among male infants, with pooled odds ratios exceeding 1.2 across multiple geographic regions. Similarly, Hoyek et al. [65] observed that males constituted approximately 55–60% of infants requiring laser or anti-VEGF therapy. The lack of a significant gender association in our study may be due to the limited sample size and the relatively small number of severe ROP cases.

Gestational Age and Risk of Retinopathy of Prematurity

The mean gestational age (GA) in our study was 31.0 ± 1.7 weeks, with the majority of neonates belonging to the 28–30 weeks (41.3%) and 31–32 weeks (26.3%) gestational age groups. This distribution is comparable to several published studies evaluating preterm populations at risk of adverse neonatal outcomes. In the Turkish cohort, non-ROP infants had a higher mean GA of 32 weeks (range 26–35), whereas infants with ROP had a significantly lower mean GA of 29 weeks (range 23–35) ($p < 0.001$). Similarly, Wang et al. [63] reported a mean GA of 30.7 ± 1.71 weeks among preterm twins, with infants developing ROP having a lower GA of 28.56 ± 1.82 weeks compared to 31.35 ± 1.54 weeks in non-ROP infants ($p < 0.001$). The relatively higher mean GA observed in our cohort may show a comparatively lower proportion of extremely preterm infants, which could influence the overall risk profile and neonatal outcomes.

In the present study, infants with ROP had significantly lower gestational age (30.38 ± 1.86 weeks) compared to those without ROP (31.30 ± 1.61 weeks, $p = 0.027$), along with substantially lower birth weight (1.25 ± 0.29 kg vs. 1.71 ± 0.28 kg, $p < 0.001$). Wang et al. [63], in a discordant twin-pair analysis, similarly reported that infants with ROP had a lower mean gestational age of 28.56 ± 1.82 weeks compared to 31.35 ± 1.54 weeks in non-ROP twins and a lower mean birth weight of 1104 g versus 1671 g ($P < 0.001$). Importantly, Wang et al. [63] further showed that within twin pairs matched for gestational age, birth weight alone did not independently predict ROP, confirming gestational age ≤28 weeks as the dominant determinant. In the same study, severe ROP cases exhibited even lower values, with a mean gestational age of 27.75 ± 1.58 weeks and mean birth weight of 1073 g. Consistent with these findings, CRYO-ROP data cited by Wang et al. [63] reported ROP incidence rates approaching 80–83% among infants born at ≤28 weeks or weighing <1000 g. The significantly lower gestational age and birth weight observed among ROP cases in our cohort further corroborate immaturity as the strongest predictor of ROP development.

The majority of neonates in the 28–34 weeks gestational age range in our study is consistent with multicenter observations by Klevebro et al. [66], who evaluated 2521 preterm infants born between 23 and 30 weeks. In their study, infants born at lower gestational ages (23–26 weeks) had markedly lower median birth weights (595–890 g) and significantly higher rates of severe ROP (up to 58.1%) compared to those born at 27–30 weeks, where ROP ≥ stage 3 ranged from 0.9% to 9.2%. Our cohort, with a higher mean GA and BW, falls closer to the later gestational age groups described by Klevebro et al.[66], which are associated with lower morbidity rates.

Gestational age showed a clear inverse relationship with ROP occurrence in our study, although statistical significance was not achieved ($p = 0.121$). A higher proportion of ROP cases occurred in the 28–30 weeks gestational age group (58.3%) compared to more mature infants. This trend is consistent with robust evidence from previous studies. A large meta-analysis reported that the odds of developing ROP increase by approximately 1.4 times for each one-week reduction in gestational age, with infants born at 23 weeks facing a 66.5% risk of ROP and a 40.3% risk of severe disease. Wu et al.[67], in a twin-pair study, showed significantly higher ROP rates among infants born at ≤28 weeks compared to those born later, independent of birth weight. The absence of statistical significance in our findings may show the relatively narrow gestational age range and smaller number of extremely preterm infants.

Birth Weight as a Determinant of Retinopathy of Prematurity

In the present study, the mean birth weight (BW) was 1.57 ± 0.35 kg, with two-thirds of infants (66.3%) weighing between

1.5 and 2.0 kg, while only 10.0% belonged to the extremely low birth weight (<1.0 kg) category. These findings are comparable to previously reported data, though some studies included a higher proportion of lower birth weight infants. The Turkish study documented a mean BW of 1700 g (range 820–2830 g) in non-ROP infants and 1180 g (range 490–2850 g) in ROP infants, showing a significant inverse relationship between BW and adverse outcomes ($p < 0.001$). Wang et al.[63] reported a mean BW of 1104 g among ROP infants compared to 1671 g in non-ROP infants, with severe ROP cases having a mean BW as low as 1074 g. Compared to these studies, the higher mean BW in our cohort shows a relatively more mature neonatal population, which may partly explain differences in morbidity patterns.

In the present study, gestational age and birth weight showed a significant association with ROP severity, with mean gestational age decreasing from 31.30 ± 1.61 weeks in infants without ROP to 29.67 ± 1.80 weeks in Stage 1 and 30.43 ± 2.07 weeks in Stage 2, while mean birth weight declined progressively from 1.71 ± 0.28 kg in non-ROP infants to 1.16 ± 0.22 kg in Stage 3 ROP ($p = 0.045$ for gestational age and $p < 0.001$ for birth weight). These findings show that although gestational age shows some overlap across stages, birth weight declines more consistently with increasing ROP severity. Similar observations were reported by Z.H. Wang et al. [63] in a twin-pair study, where infants with ROP had significantly lower mean gestational age (28.56 ± 1.82 weeks) and birth weight (1104 g) compared to non-ROP controls (31.35 ± 1.54 weeks and 1671 g) and infants with severe ROP had even lower values (27.75 ± 1.58 weeks and 1073 g). Another cohort study reported that Stage 1 ROP majorly occurred in infants born at 29–32 weeks with birth weight between 1000–1500 g, whereas Stage 3 or higher ROP clustered among infants born at ≤28 weeks with birth weight <1000 g. The statistically significant differences across stages in our study reinforce the role of immaturity, particularly low birth weight, in determining disease severity.

Birth weight showed a strong and statistically significant association with ROP in our cohort ($p < 0.001$). Infants weighing less than 1.0 kg constituted 20.8% of ROP cases compared to only 5.4% among those without ROP, while 80.4% of neonates without ROP weighed ≥1.5 kg. This observation strongly supports existing literature identifying low birth weight as a major risk factor for ROP. Large registry-based studies have reported ROP incidences ranging from 30% to 50% among very low birth weight infants, with rates rising sharply below 1000 g. Löfqvist et al. [68] further showed that low birth weight standard deviation scores and small-for-gestational-age status independently increased the risk of severe ROP requiring treatment. Although Wu et al. [67] noted that birth weight effects may be mediated by gestational age in twin analyses, the significant association observed in our study shows birth weight as an important and practical screening criterion.

When categorized by birth weight, our findings further are similar to published evidence that lower birth weight is associated with increased neonatal risk. Bing Wang et al.[63], in a study of 107 preterm infants, reported that infants weighing <1000 g had a mean GA of 28.4 ± 0.9 weeks and higher incidences of late-onset sepsis (44.4%) and periventricular-intraventricular hemorrhage (60.0%), along with a lower survival rate (77.8%). In contrast, infants weighing 1250–1500 g had a higher mean GA of 30.8 ± 4.2 weeks and a survival rate of 95.1%. In comparison, the majority of infants in the 1.5–2.0 kg group in our study shows a comparatively favorable baseline risk profile.

A strong inverse correlation was observed between birth weight and ROP stage severity in the present study ($r = −0.598$, $p < 0.001$), showing that lower birth weight is associated with progression to more advanced ROP stages. This finding is consistent with population-based data reported by Lindgren et al.[69], who showed that weight at first ROP detection was a strong predictor of severity, with median birth weight of 1540 g in non-treatment ROP compared to 1995 g in treatment-requiring cases ($p < 0.001$) and a significantly lower weight standard deviation score (−2.19) among severe ROP cases compared to milder disease (−1.18). Similarly, Wang et al. [63] reported mean birth weights of 1671 g in non-ROP infants, 1104 g in infants with any ROP and 1073 g in those with severe ROP, with differences remaining statistically significant ($p < 0.001$). These observations show that while gestational age determines baseline vulnerability, lower birth weight amplifies disease progression, possibly through impaired postnatal growth and reduced retinal vascular resilience.

Association of Septicemia with Retinopathy of Prematurity

In the present study, septicemia showed a statistically significant association with Retinopathy of Prematurity, with 79.2% of neonates with ROP having documented sepsis compared to 51.8% among those without ROP ($p = 0.022$). This finding is consistent with strong evidence from previous studies showing neonatal sepsis as a major risk factor for ROP development. A systematic review and meta-analysis by Chen et al.[70], encompassing 16 studies and 12,466 preterm infants, showed that sepsis increased the odds of any-stage ROP by 57% (OR = 1.57; 95% CI: 1.31–1.89) and more than doubled the risk of severe ROP (OR = 2.33; 95% CI: 1.21–4.51). Similarly, Allegaert et al.[71], in a large cohort of very preterm infants, reported a dose-dependent increase in treatment-warranted ROP with recurrent culture-proven sepsis episodes, particularly among infants born at <29 weeks gestation. The significant association observed in our study supports the hypothesis that systemic inflammation, oxidative stress and cytokine-mediated endothelial injury during sepsis contribute to abnormal retinal vascular development.

Association of Anemia with Retinopathy of Prematurity

In contrast to sepsis, anemia did not show a statistically significant association with ROP in our cohort, with anemia present in 20.8% of ROP cases and 16.1% of non-ROP cases ($p = 0.607$). This finding differs from several published reports identifying anemia as an independent risk factor for ROP. Lundgren et al.[72], in a prospective study of 227 extremely preterm infants (<28 weeks gestation), reported that prolonged anemia (hemoglobin <110 g/L) during the first postnatal week independently predicted treatment-requiring ROP, with an overall incidence of 11%. Similarly, Thomas et al.[73] observed anemia as a significant contributor to ROP development in preterm neonates with gestational age <35

weeks and birth weight <2 kg. The lack of statistical significance in our study may be attributed to the smaller proportion of severely anemic infants, differences in anemia definitions, or effective early correction practices in the study setting. These findings show that anemia-related ROP risk may be more pronounced in extremely preterm or severely anemic populations.

Association of Blood Transfusion with Retinopathy of Prematurity

Blood transfusion showed a strong and statistically significant association with ROP in the present study, with 75.0% of infants with ROP receiving transfusions compared to 37.5% of those without ROP ($p = 0.002$). This observation is in concordance with extensive literature identifying transfusion exposure as a major modifiable risk factor for ROP. Wang et al. [63], in a multicenter cohort study of 832 very preterm infants, reported that red blood cell transfusion within the first four weeks of life significantly increased the risk of ROP (adjusted OR = 1.70; 95% CI: 1.14–2.53) and ≥stage 2 ROP (adjusted OR = 1.68), with risk escalating with the number and volume of transfusions ($P < 0.001$ for trend). Additionally, Teofili et al. [74] found that early transfusion, particularly before a postmenstrual age of 28 weeks, was strongly predictive of severe ROP (OR = 6.57). The significant association observed in our study reinforces the role of transfusion-related oxidative stress and altered oxygen delivery in retinal vascular dysregulation.

Association of Mode of Delivery with Retinopathy of Prematurity

In the present study, the mode of delivery showed no significant association with ROP occurrence, with comparable proportions of vaginal delivery among ROP (41.7%) and non-ROP infants (42.9%) ($p = 0.921$). This finding is similar to several studies reporting no independent effect of delivery mode after adjustment for gestational age and birth weight. However, contrasting evidence exists in the literature. A meta-analysis by Sumual et al. [75], including 2048 preterm infants from five cohort studies, reported lower ROP incidence among infants delivered by caesarean section, with an unadjusted odds ratio of 0.54 (95% CI: 0.40–0.73), although the association lost significance after adjustment (adjusted OR = 0.59; 95% CI: 0.28–1.23). In contrast, Manzoni et al. [76], studying extremely low birth weight infants (<1000 g), reported a significantly higher rate of threshold ROP among vaginally delivered neonates (40.9%) compared to those delivered by caesarean section (17.5%), with a relative risk of 3.35 ($p = 0.008$). The absence of a significant association in our study may show the relatively lower proportion of extremely low birth weight infants and shows that mode of delivery alone may not independently influence ROP risk in moderately preterm populations.

Duration of Oxygen Supplementation and Retinopathy of Prematurity

In the present study, preterm neonates who developed Retinopathy of Prematurity required significantly longer oxygen supplementation compared to those without ROP (4.00 ± 3.20 days vs. 2.21 ± 2.56 days, $p = 0.010$), showing the role of prolonged oxygen exposure in ROP pathogenesis. Estrada et al. [77] showed that each additional day of supplemental oxygen exposure with FiO_2 >21% during the first 28 postnatal days independently increased the risk of severe ROP and the inclusion of oxygen duration significantly improved screening accuracy beyond gestational age and birth weight alone. Similarly, Chen et al. [78], in a meta-analysis, reported that maintaining lower oxygen saturation targets (70–96%) during early postnatal life reduced the risk of severe ROP by 52% (RR = 0.48, 95% CI 0.31–0.75), whereas prolonged exposure to higher saturation levels (>94%) in later weeks significantly increased ROP progression. The longer duration of oxygen supplementation observed among ROP cases in our study supports these findings and showes the importance of cautious oxygen administration.

Oxygen Supplementation Duration According to ROP Severity

A significant stepwise increase in oxygen supplementation duration was observed with increasing ROP severity in the present study, with mean durations of 2.21 ± 2.56 days in infants without ROP, 2.22 ± 2.95 days in Stage 1, 3.43 ± 2.94 days in Stage 2 and 6.50 ± 2.20 days in Stage 3 ROP ($p < 0.001$). Teoh et al.[79], in a prospective study involving very low birth weight infants, reported that infants with ROP had a mean oxygen therapy duration of 9.4 days, with regression analysis showing a sharp increase in ROP probability beyond five days of oxygen exposure and exceeding 90% at approximately 30 days. Flynn et al. [80], referencing findings from the STOP-ROP trial, observed that infants progressing to threshold ROP experienced significantly longer exposure to high-saturation oxygen (SpO_2 >94%) compared to non-progressors. Similarly, Chen et al. [70] reported that severe ROP (Stage 3 or higher) was majorly associated with prolonged or cumulative oxygen exposure exceeding 20–30 days. The progressive increase in oxygen duration across ROP stages in our study similar to these observations and reinforces oxygen exposure as a key determinant of disease severity.

Correlation Between Oxygen Supplementation Duration and ROP Stage

In the present study, the duration of oxygen supplementation showed a moderate positive correlation with ROP stage severity ($r = 0.412$, $p < 0.001$), showing that prolonged oxygen exposure is associated with progression to higher ROP stages. This finding is similar to the results of Praveen et al. [81], who reported significantly longer mean oxygen therapy duration among infants with ROP (16.78 ± 7.85 days) compared to those without ROP (9.22 ± 5.89 days), with higher stages associated with cumulative exposure exceeding 14 days. Flynn et al. [80], in their analysis of the STOP-ROP trial, further showed that infants progressing to threshold ROP experienced prolonged exposure to high oxygen saturation levels, with median durations exceeding 20 days at SpO_2 >94%, compared to approximately 10–14 days among infants with regressing Stage 1 disease. Chen et al. [78] similarly showed that extended duration and higher concentration of oxygen supplementation amplify hyperoxia-induced retinal vascular arrest, increasing the likelihood of severe ROP. The positive correlation observed in our study supports the role of oxygen exposure as a key modifiable risk factor influencing ROP severity.

Integrated Interpretation of ROP Severity Determinants

The combined analysis of gestational age, birth weight and oxygen supplementation in the present study showes that ROP severity is driven by a complex interaction between immaturity at birth and postnatal environmental exposures. While gestational age shows intrinsic developmental vulnerability, birth weight shows a stronger and more consistent inverse relationship with disease severity and prolonged oxygen supplementation further accelerates progression to advanced stages. Evidence from studies by Wang et al.[63], Lindgren et al.[69], Praveen et al.[81] and Flynn et al.[80] consistently supports this multifactorial model of ROP pathogenesis. These findings show the importance of early identification of high-risk infants, strict oxygen monitoring protocols and close surveillance of growth patterns to prevent progression to severe, vision-threatening ROP.

1. CONCLUSION

This study shows that retinopathy of prematurity remains a significant morbidity among preterm neonates, with an overall incidence of 30% in the study population. Lower gestational age and, more importantly, lower birth weight emerged as the strongest and most consistent risk factors for the development and increasing severity of ROP. Neonates weighing less than 1.5 kg and those born at earlier gestational ages were significantly more likely to develop ROP and progress to higher stages. Systemic factors like septicemia and the need for blood transfusion were also significantly associated with ROP, showing that overall neonatal illness severity plays an important contributory role. Prolonged oxygen supplementation showed a clear dose–response relationship, with both the occurrence and severity of ROP increasing with longer duration of oxygen exposure. In contrast, gender, anemia and mode of delivery did not show a significant association with ROP. The strong negative correlation between birth weight and ROP stage, along with the positive correlation between oxygen duration and ROP stage, shows the multifactorial nature of ROP. These findings show the need for meticulous monitoring of high-risk preterm infants, judicious use of oxygen therapy, early screening and prompt intervention to prevent progression to severe stages of retinopathy of prematurity and reduce the risk of long-term visual impairment.

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