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Original Research Article

Study of retinopathy of prematurity in neonates admitted to a neonatal intensive care unit: a prospective observational study

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina and a leading cause of preventable childhood blindness. With improving neonatal survival in resource-limited settings, the burden of ROP is rising. To determine the incidence and identify maternal and neonatal risk factors of ROP in neonates admitted to a tertiary care neonatal intensive care unit (NICU).
Methods: A prospective observational study was conducted over 18 months (July 2023-July 2025). Sixty-eight neonates meeting eligibility criteria were enrolled. ROP screening was performed by indirect ophthalmoscopy following NNF guidelines.
Results: ROP incidence was 33.8%, 82.6% had mild ROP (stages 1-3) and 17.4% had severe ROP. Pregnancy-induced hypertension (PIH) was the only significant maternal risk factor (p=0.002). Significant neonatal risk factors included gestational age 28-32 weeks and birth weight 1-1.5 kg (both p<0.001), respiratory distress syndrome (p=0.001), apnea (p=0.002), sepsis (p=0.011), necrotising enterocolitis (p=0.001), culture-positive sepsis (p=0.004), mechanical ventilation (p=0.003), non-invasive ventilation (p=0.006), surfactant therapy (p=0.002), and blood transfusion (p=0.001). Among neonates with ROP, apnea was the sole predictor of severe disease (p=0.024). All four severe ROP cases received laser photocoagulation; in addition, two babies also required anti-VEGF therapy.
Conclusions: ROP incidence was 33.8%, consistent with Indian tertiary-centre reports. Prematurity, low birth weight, PIH, sepsis, RDS, NEC, apnea, ventilatory support, and blood transfusion are key risk factors. Apnea is a significant predictor of severe ROP. Timely screening and management of modifiable risk factors are essential to reduce ROP-associated blindness.

Keywords: Retinopathy of prematurity, Preterm neonate, NICU, Risk factors, Low birth weight, Sepsis, Apnea

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina that predominantly affects premature neonates.[1,2] It develops from disrupted retinal vascular development when an infant is born before retinal vascularisation is complete. Retinal vascularisation normally completes at approximately 36 weeks on the nasal side and 40 weeks on the temporal side.[3,4] When prematurity interrupts this process, initially there is vascular attenuation followed by aberrant fibrovascular proliferation which can result in traction and retinal detachment, causing severe or permanent visual impairment.[3,4]

In India, due to improvements in facility-based neonatal care there is marked increase in the survival of very preterm and very low birth weight infants, leading to increase in risk for ROP.[5] Recent Indian studies have reported ROP in 20-32.3% of screened neonates, rates vary considerably between institutions depending on gestational age thresholds, oxygen management practices, and screening compliance.[5,6] ROP is clinically silent in its early stages, making systematic screening the only reliable method for timely detection.[7,8]

The disease carries substantial individual and societal costs. Beyond blindness, severe visual impairment interferes with motor, language, cognitive, and social development, burdens that intensify once the child enters formal education.[1,2] Effective screening, followed by timely treatment with laser photocoagulation or intravitreal anti-VEGF therapy if indicated, can prevent these outcomes.[7,8] The primary responsibility for initiating ROP screening rests with the neonatologist or paediatrician, who must refer at-risk infants to a trained ophthalmologist within defined time windows. Failure to do so carries significant medico-legal implications.[7]

Despite the clear importance of ROP surveillance, data from Indian NICUs on incidence and risk factor profiles remain heterogeneous, and single-centre prospective data from tertiary centres in Maharashtra are limited.[5,6] This study was therefore undertaken to determine the incidence of ROP and to identify the maternal and neonatal risk factors that predispose neonates admitted to a tertiary care NICU to developing ROP.

METHODS

Study design and setting

This was a prospective observational study conducted in the neonatal intensive care unit (NICU) of the Department of Paediatrics at a Tertiary Care Hospital in Maharashtra, India, between July 2023 and July 2025.

Study population and eligibility

Inclusion criteria

All neonates admitted to the NICU during the study period were considered for enrolment. Inclusion criteria followed the Rashtriya Bal Swasthya Karyakram (RBSK) recommendations.[9] Gestational age less than 34 weeks or birth weight less than 2000 g; or gestational age 34-36 weeks with at least one of the following risk factors - need for respiratory support, oxygen therapy for more than six hours, sepsis, episodes of apnea, need for blood or exchange transfusion, respiratory distress syndrome, intraventricular haemorrhage, or congenital heart disease were included.

Exclusion criteria

Neonates whose guardians declined participation were excluded.

ROP screening protocol

Pupillary dilatation was achieved using a combination of tropicamide 0.8% and phenylephrine 5% diluted 1:1 in distilled water, administered as one drop three times at 10-minute intervals, 30 minutes before examination. Retinal examination was performed by a trained retinal specialist using binocular indirect ophthalmoscopy.[7,8] The first examination was scheduled at four weeks of postnatal age for most eligible neonates; for those born at less than 28 weeks gestation or weighing less than 1200 g, the first examination was advanced to two to three weeks of postnatal age to enable early detection of aggressive posterior ROP.[9,10] Follow-up examinations were conducted according to the National Neonatology Forum of India schedule until full retinal vascularisation reached zone 3 or until ROP regressed following treatment. ROP present in either or both eyes was counted as a single case.[10]

Classification and definitions

ROP was classified according to the international classification of retinopathy of prematurity (ICROP).[4] Mild ROP was defined as stages 1-3 without plus disease or aggressive posterior ROP (APROP). Severe ROP encompassed stage 4 or 5, plus disease, or APROP.[3,4]

Data collection

Detailed maternal and neonatal data were recorded prospectively using a structured proforma. Maternal variables included age, parity, antenatal history, gestational age, mode of delivery, and risk factors such as pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), multiple gestation, and antenatal steroid administration. Neonatal variables included sex, birth weight, gestational age, appropriateness for gestational age (AGA/SGA), need for resuscitation, and clinical course including respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), sepsis (clinical and culture-positive), intraventricular haemorrhage (IVH), apnea, congenital heart disease, neonatal seizures, mode and duration of ventilatory support, oxygen therapy, blood transfusion, and surfactant administration.

Statistical analysis

Data on categorical variables are presented as frequency and percentage. Continuous variables are expressed as mean±standard deviation. The Chi-square test was used to compare categorical variables between ROP and non-ROP groups, and between mild and severe ROP groups. The independent-samples t-test was applied for continuous variables.

A p value of less than 0.05 was considered statistically significant. All analyses were performed using statistical package for the social sciences (SPSS) version 26.0 (IBM corporation, New York, USA).

Ethical considerations

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from the parents or legally acceptable representatives of all enrolled neonates prior to enrolment.

RESULTS

Baseline characteristics

A total of 68 neonates were screened during the study period.

Table 1: Baseline demographic and clinical characteristics of the study population (n=68).

Characteristics	N	%
Sex		
Female	39	57.4
Male	29	42.6
Gestational age at birth (weeks)		
<28	4	5.8
28-32	33	48.6
>32	31	45.6
Birth weight (kg)		
<1	8	11.8
1-2	51	75.0
>2	9	13.2
Birth weight for gestational age		
AGA	58	85.3
SGA	10	14.7
Mode of delivery		
LSCS	46	67.6
NVD	22	32.4
Maternal factors		
PIH	27	39.7
GDM	4	5.9
Multiple pregnancy	23	33.8
Antenatal steroids received by mother	57	83.8

PIH=pregnancy-induced hypertension; GDM=gestational diabetes mellitus

Table 2: Incidence and grading of ROP.

ROP	Frequency	Percent
Present	23	33.8
Absent	45	66.2
Total	68	100.0
ROP grade		
Mild	19	82.6
Severe	4	17.4
Total	23	100.0
Treatment for ROP		
Laser photocoagulation	4	100% of severe
Combination anti-VEGF therapy	2	50% of severe

ROP was diagnosed in 23 of 68 neonates (33.8%). Of these, 19 (82.6%) had mild ROP and 4 (17.4%) had severe ROP.

All four severe cases received laser photocoagulation; two additionally required anti-VEGF therapy.

Table 3: Comparison of maternal risk factors between ROP and non-ROP groups.

Maternal risk factors	ROP (n=23)	No ROP (n=45)	P value
PIH - yes	15	12	0.002*
PIH - no	8	33	
Multiple pregnancy	7	16	0.673
GDM	3	1	0.109
Antenatal steroids - yes	22	35	0.083
LSCS	15	31	0.759

*Statistically significant (p<0.05). PIH=pregnancy-induced hypertension; GDM=gestational diabetes mellitus

PIH was present in 27 mothers (39.7%) and was the only maternal factor significantly associated with ROP (p=0.002).

Mean GA was significantly lower in the ROP group (29.98±1.97 versus 33.09±2.25 weeks, p<0.001). All four neonates born at <28 weeks developed ROP; none born at >34 weeks did.

Mean birth weight was also lower in the ROP group (1167±286 g versus 1661±410 g, p=0.001). The 1-1.5 kg category accounted for 60.9% of ROP cases; no neonate >2 kg developed ROP.

Table 4: Neonatal characteristics: ROP versus non-ROP groups.

Variables	ROP (n=23), N (%)	No ROP (n=45), N (%)	P value
Mean GA (weeks) ±SD	29.98±1.97	33.09±2.25	<0.001*
GA <28 weeks	4 (17.4)	0 (0)	<0.001*
GA 28-32 weeks	16 (69.6)	17 (37.8)	
GA 32-34 weeks	3 (13.0)	9 (20.0)	
GA >34 weeks	0 (0)	19 (42.2)	
Mean BW (g) ±SD	1167.30±286.48	1661.15±410.41	0.001*
BW <1 kg	7 (30.4)	1 (2.2)	0.001*
BW 1-1.5 kg	14 (60.9)	24 (53.3)	
BW 1.5-2 kg	2 (8.7)	11 (24.4)	
BW >2 kg	0 (0)	9 (20.0)	
Female sex	13 (56.5)	26 (57.8)	0.921
SGA	60% of ROP	40% of ROP	>0.05

*Statistically significant (p<0.05)

Table 5: Comparison of neonatal risk factors between ROP and non-ROP groups.

Neonatal risk factors	ROP (n=23), N (%)	No ROP (n=45), N (%)	P value
RDS	21 (91.3)	18 (40.0)	0.001*
Apnea	10 (43.5)	2 (4.4)	0.002*
Sepsis (clinical)	21 (91.3)	28 (62.2)	0.011*
Culture-positive sepsis	10 (43.5)	1 (2.2)	0.004*
NEC	17 (73.9)	6 (13.3)	0.001*
Mechanical ventilation	17 (73.9)	10 (22.2)	0.003*
Non-invasive ventilation (NIV)	23 (100)	24 (53.3)	0.006*
Surfactant received	18 (78.3)	12 (26.7)	0.002*
Blood transfusion	21 (91.3)	8 (17.8)	0.001*
Resuscitation required	21 (91.3)	31 (68.9)	0.115
IVH	5 (21.7)	3 (6.7)	0.109
CHD	6 (26.1)	4 (8.9)	0.076
Neonatal seizures	4 (17.4)	2 (4.4)	0.152

*Statistically significant ($p<0.05$). RDS=respiratory distress syndrome; NEC=necrotising enterocolitis; IVH=intraventricular haemorrhage; CHD=congenital heart disease

Table 6: Comparison of neonatal risk factors: mild versus severe ROP (n=23).

Neonatal risk factors	Mild ROP (n=19), N (%)	Severe ROP (n=4), N (%)	P value
Apnea	6 (31.6)	4 (100)	0.024*
RDS	17 (89.5)	4 (100)	1.000
Sepsis	17 (89.5)	4 (100)	1.000
NEC	13 (68.4)	4 (100)	0.539
Blood transfusion	17 (89.5)	4 (100)	1.000
Mechanical ventilation	14 (73.7)	3 (75.0)	1.000
Culture-positive sepsis	9 (47.4)	1 (25.0)	0.604
IVH	5 (26.3)	0 (0)	0.539
Neonatal seizures	3 (15.8)	1 (25.0)	0.679

*Statistically significant ($p<0.05$)

DISCUSSION

Incidence

The incidence of ROP in our study was 33.8%, consistent with Indian and international studies. Freitas et al (Brazil) reported 33.9%, and Ahuja et al (South India) 32.6% higher rates (52-66%) in some series reflect greater proportions of extremely preterm infants.[11-14] The heterogeneity in published incidence rates reflects differences in gestational age distributions, screening criteria, oxygen management practices, and institutional resources, underscoring the importance of institution-specific data to guide local screening programmes.[1,5,15]

Severity and treatment

The 82.6% mild/17.4% severe split aligns with Singh et al (78.6%/21.4%) and Vasavada et al (89%/10.2%) and likely reflects the benefit of regular serial screening, permitting timely intervention before disease progression.[16,17] All four severe cases received laser photocoagulation - the gold standard - and two additionally required anti-VEGF therapy, appropriate for zone 1 or APROP where laser alone may be insufficient.[3,4]

Maternal risk factors

PIH was the only significant maternal risk factor ($p=0.002$), with 55.6% of neonates from hypertensive mothers developing ROP - consistent with Chen et al (China), who identified maternal preeclampsia as an independent risk factor.[15,18] Uteroplacental insufficiency in PIH causes chronic foetal hypoxia and early delivery; additionally, PIH alters the balance of angiogenic factors (elevated sFlt-1, reduced placental growth factor), potentially predisposing neonates to abnormal retinal vascularisation. Multiple gestation, GDM, and antenatal steroids were not significant, though sample size limits power to detect modest associations. Sabzehei et al reported multiple gestation as an independent predictor of ROP, while Debnath et al found antepartum haemorrhage and prolonged rupture of membranes to be significant maternal risk factors.[19,20]

Gestational age and birth weight

Both lower GA and lower BW were strongly associated with ROP, consistent with the established literature.[1,2,6] The inverse relationship between GA and ROP incidence (all <28-week neonates affected, none >34 weeks) reflects the fundamental biology: earlier birth means more immature avascular peripheral retina and more prolonged exposure to hyperoxia and growth factor deficiency.[3,4,15]

Mean birth weight in the ROP group (1167 g) aligns closely with Anjali et al (1160 g) and Sabzehei et al no neonate >2 kg developed ROP.[19,21] Low birth weight neonates are prone to ROP due to immature retinal vessels, insufficient antioxidant reserves, and prolonged dependence on supplemental oxygen.[6,15]

Neonatal morbidities as risk factors

Blood transfusion (91.3% versus 17.8%, $p=0.001$) generates reactive oxygen species via iron loading and free haemoglobin; additionally, adult haemoglobin in transfused blood releases oxygen more readily than foetal haemoglobin, potentially causing relative hyperoxia at the

retinal level - findings echoed by Gupta et al and Dani et al.[6,22]

RDS, sepsis, NEC, ventilatory support, surfactant, and blood transfusion were all significantly more common in the ROP group, consistent with and extend the existing literature from Indian and international NICUs.[6,15,19,21,23,24]

NEC and ROP share common risk factors (extreme prematurity, systemic inflammation), and emerging evidence suggests NEC-associated cytokine release may independently promote pathological retinal angiogenesis.[15,22]

Culture-positive sepsis (p=0.004) conferred greater risk than clinical sepsis alone, likely reflecting more severe inflammatory and endothelial disruption. Supplemental oxygen, near-universal in the ROP group, did not independently reach significance - partly because quantitative FiO_2 and SpO_2 duration data were unavailable. Shah et al and Shahidullah et al similarly identified sepsis and prolonged oxygen administration as significant contributors to ROP.[23,24]

In RDS surfactant requirement and mechanical ventilation rates were also significantly higher in the ROP group. These observations reflect the profound prematurity of the ROP cohort and the associated need for intensive respiratory support.[1,21]

The intermittent hypoxaemia associated with apnoeic episodes is a potent stimulus for VEGF upregulation, and repeated fluctuations between hypoxia and hyperoxia may accelerate the neovascular phase of ROP.[3,4,20]

Apnea as a predictor of severe ROP

The most clinically important finding is that apnea was the sole significant predictor of severe ROP (p=0.024). Repetitive hypoxia-reoxygenation cycles during apnoeic episodes upregulate VEGF via HIF-1α and HIF-2α, driving pathological neovascularisation.[3,4]

This corroborates Verma et al (2015), who identified apnea as an independent predictor of severe ROP, and Debnath et al (2024), who found apnea carried the highest odds ratio among neonatal risk factors (OR 4.35, 95% CI 1.08-17.55).[20,25] Vigilant apnea monitoring and prompt caffeine therapy may therefore reduce progression to severe ROP beyond their established respiratory benefits.

Limitations

This was a single-centre study of 68 neonates, limiting generalisability and power for multivariate analysis. Quantitative oxygen exposure data (FiO_2, SpO_2 duration) were not captured. Long-term visual outcomes were not assessed. Larger multi-centre prospective studies with extended follow-up are warranted.

CONCLUSION

ROP incidence was 33.8% in this prospective NICU cohort, with most cases mild and amenable to treatment or spontaneous regression. PIH was the only significant maternal risk factor. Lower gestational age and birth weight, RDS, apnea, sepsis, NEC, ventilatory support, surfactant therapy, and blood transfusion were significant neonatal predictors. Critically, apnea was the sole determinant of severe ROP.

To reduce the burden of ROP-related blindness, a multi-pronged approach is required: universal screening per RBSK and NNF guidelines. Prompt management of modifiable risk factors, especially sepsis, apnea, and NEC. Judicious oxygen management targeting SpO_2 90-95%.[15] Promotion of early exclusive breast milk feeding.[22] Enhanced neonatologist training in ROP awareness and referral pathways.

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