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Original Article

Spectrum of Retinopathy of Prematurity in Preterm Small for Gestational Age Neonates

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a major preventable cause of childhood visual impairment in premature infants, with risk influenced by gestational maturity and neonatal morbidity. Data focused on high-risk preterm small-for-gestational-age (SGA) infants can inform screening and care priorities.
Objectives: To estimate the proportion (incidence) of development of ROP in preterm SGA babies.
To identify the risk factors contributing to the development of ROP in preterm SGA babies.
Methods: This hospital-based prospective study included 100 preterm SGA babies with gestational ages less than 37 weeks. The babies were screened for ROP using standardized protocols. Data on gestational age, birth weight, respiratory support, sepsis, anemia, and other maternal and neonatal factors were collected. Statistical analyses were performed to determine the correlation between these factors and the severity of ROP.
Results: The overall incidence of ROP (either eye) was 40%. Stage distribution was identical in both eyes: No ROP 60%, Stage 1 10%, Stage 2 25%, and Stage 3 5%. Plus disease was present in 6% of eyes and pre-plus in 1%; APROP occurred in 5% of right eyes and 4% of left eyes. Zone distribution showed Zone 1 14%, Zone 2 25%, and Zone 3 1% of eyes (with the remainder having no ROP). Most infants required no active treatment (85%); laser was used in 12% and anti-VEGF in 3%. Follow-up was most commonly 7 visits (32%). Final outcome was recorded as resolved in 96% and death in 4%. Reported risk-factor associations included mechanical ventilation (61%; p=0.015), oxygen therapy (100%; p=0.025), RDS (40%; p=0.020), sepsis (20%; p=0.045), CLD (12%; p=0.048), anaemia (31%; p<0.050), maternal hypertension (40%; p=0.035) and preeclampsia (20%; p=0.022).
Conclusion: In preterm SGA infants, ROP incidence was 40%, with predominantly mild-to-moderate disease and a minority requiring treatment. Higher risk clustered with prematurity-related morbidity—particularly respiratory support variables and anaemia—underscoring the importance of rigorous screening and follow-up in this high-risk population.

Keywords*: retinopathy of prematurity; small for gestational age; prematurity; risk factors; screening.*

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina and remains a leading, preventable cause of childhood blindness. With improving survival of preterm infants, the burden of ROP screening and treatment continues to rise, particularly in neonatal intensive care settings where screening coverage, workforce training,

and follow-up practices can vary. Effective screening programs depend on the timely identification of at-risk infants and consistent examination protocols, supported by trained personnel and standardised workflows.

The pathogenesis of ROP is closely linked to the normal sequence of retinal vascular development and its disruption by premature birth. Prematurity interrupts physiologic retinal vascularisation and exposes the immature retina to fluctuating oxygen levels and systemic stressors, leading to dysregulated angiogenic signalling and, in some infants, pathologic neovascularisation. Experimental and mechanistic work has highlighted the central role of vascular endothelial growth factor (VEGF) and oxygen-mediated pathways in shaping normal vascular growth and oxygen-induced retinopathy, providing the biological rationale for modern prevention strategies and targeted therapies.

Clinically, ROP detection relies on structured screening examinations. Program quality is influenced by the accuracy and reliability of screening—whether performed by indirect ophthalmoscopy or imaging-based approaches—making operator training and standardisation critical. In addition to classic ROP findings, non-ROP–related fundus haemorrhages may occur in preterm infants and can complicate screening interpretation by obscuring the retinal view or mimicking disease activity, which can affect follow-up decisions.

Management of ROP is guided by disease severity and risk of progression. Laser photocoagulation remains an established treatment for sight-threatening disease, while anti-VEGF therapy is used selectively, particularly for posterior disease patterns, and requires careful follow-up due to recurrence risk and evolving vascularisation. Given these clinical and programmatic demands, determining the incidence, severity profile, and associated risk factors in specific high-risk groups—such as preterm small-for-gestational-age infants—can help refine screening strategies, improve resource allocation, and strengthen treatment pathways within local neonatal care systems.

AIM AND OBJECTIVES

Aim

To evaluate and study the risk factors associated with the development of retinopathy of prematurity (ROP) in preterm small-for-gestational-age (SGA) babies.

Objectives

To estimate the proportion (incidence) of development of ROP in preterm SGA babies.
To identify the risk factors contributing to the development of ROP in preterm SGA babies.

METHODS :This hospital-based prospective study included 100 preterm SGA babies with gestational ages less than 37 weeks. The babies were screened for ROP using standardized protocols. Data on gestational age, birth weight, respiratory support, sepsis, anemia, and other maternal and neonatal factors were collected. Statistical analyses were performed to determine the correlation between these factors and the severity of ROP.

RESULTS

1. **Baseline characteristics of the study cohort**

Baseline demographic and perinatal characteristics are summarised in Table 1. Gestational age ranged from 26 to 36 weeks, with the largest proportion of infants born at 27 weeks (22%), followed by 35 weeks (13%) and 31 weeks (11%). Birth weight ranged from 520 to 1800 g, with the most frequent categories being 701–800 g (15%) and 801–900 g (14%).

Overall, 55% of infants were male, and 45% were female. Most were singletons (90%), and birth order was distributed as first (34%), second (37%), and third (29%) (Table 1). In the dissertation's reported analyses, gestational age and birth weight showed statistically significant associations with ROP (reported $p = 0.001$ and $p = 0.003$, respectively), whereas sex, birth order, and twin status were not reported as statistically significant (Table 1).

Table 1. Baseline characteristics of the study cohort (N = 100)

Values are n (%). Gestational age and birth weight are presented in clinically standard bands (collapsed from the dissertation's original categories).

Characteristic	n (%)
Gestational age (weeks)	
≤28 weeks	33 (33.0)
29–31 weeks	26 (26.0)
32–34 weeks	21 (21.0)
≥35 weeks	20 (20.0)
Birth weight category (g)	
<1000 (ELBW)	52 (52.0)
1000–1499 (VLBW)	39 (39.0)

≥1500	9 (9.0)
Sex	
Female	45 (45.0)
Male	55 (55.0)
Birth order	
1	34 (34.0)
2	37 (37.0)
3	29 (29.0)
Twin pregnancy	
No	90 (90.0)
Yes	10 (10.0)

ELBW = extremely low birth weight (<1000 g); VLBW = very low birth weight (1000–1499 g). Bands were derived by collapsing the original gestational-age and birth-weight distributions reported in the dissertation.

2. ROP characteristics of the study population

ROP characteristics are summarised in Table 2. Overall, 40/100 (40.0%) eyes had ROP in both the right (OD) and left (OS) eyes. The stage distribution was identical between eyes: No ROP in 60%, Stage 1 in 10%, Stage 2 in 25%, and Stage 3 in 5% of eyes.

With respect to vascular activity, plus disease was uncommon, with no plus in 93% of eyes, pre-plus in 1%, and plus disease in 6% in both OD and OS.

Zone involvement showed a similar pattern between eyes, with Zone 1 involvement in 14%, Zone 2 in 25%, and Zone 3 in 1% of eyes (in addition to the 60% with no ROP). Aggressive posterior ROP (APROP) was infrequent, present in 5% of right eyes and 4% of left eyes (Figure 1).

Table 2. ROP characteristics (N = 100 infants; 100 eyes per side)

Values are n (%). OD = right eye; OS = left eye.

Variable	OD (n=100)	OS (n=100)
Any ROP (Stage 1–3)	40 (40.0)	40 (40.0)
ROP stage		
No ROP	60 (60.0)	60 (60.0)
Stage 1	10 (10.0)	10 (10.0)
Stage 2	25 (25.0)	25 (25.0)
Stage 3	5 (5.0)	5 (5.0)
Plus disease status		
No plus	93 (93.0)	93 (93.0)
Pre-plus	1 (1.0)	1 (1.0)
Plus	6 (6.0)	6 (6.0)
ROP zone		
No ROP	60 (60.0)	60 (60.0)
Zone 1	14 (14.0)	14 (14.0)
Zone 2	25 (25.0)	25 (25.0)
Zone 3	1 (1.0)	1 (1.0)
APROP		
No	95 (95.0)	96 (96.0)
Yes	5 (5.0)	4 (4.0)

Abbreviations: ROP = retinopathy of prematurity; APROP = aggressive posterior ROP.

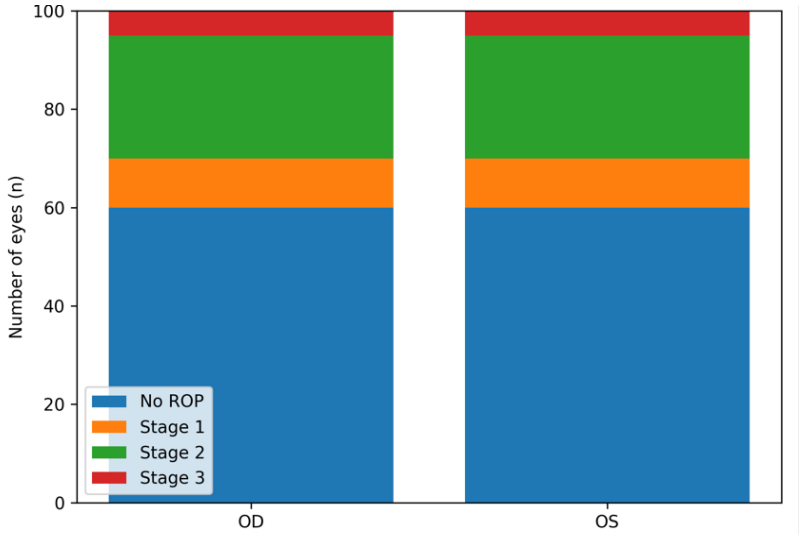

Figure 1. *ROP stage distribution by eye (OD vs OS).* Stacked bars show the distribution of retinopathy of prematurity (ROP) stages in the right eye (OD) and left eye (OS). Segments represent **No ROP**, **Stage 1, Stage 2**, and **Stage 3**; values are expressed as the **number of eyes**

3. Management, follow-up, and outcomes

Management and outcomes are summarised in Table 3. The majority of infants did not require active treatment for ROP (85/100; 85.0%). Among those treated, laser therapy was administered in 12/100 (12.0%), and anti-VEGF therapy in 3/100 (3.0%).

Follow-up intensity varied across the cohort. The most frequent follow-up pattern was 7 visits (32/100; 32.0%), followed by 2 visits (17.0%), 3 visits (14.0%), and 4 visits (11.0%); smaller proportions completed 1 visit (7.0%), 5 visits (10.0%), or 6 visits (9.0%).

At final assessment, 96/100 (96.0%) infants were documented as having resolved disease status, while 4/100 (4.0%) infants died during the study period.

Table 3. Management, follow-up, and outcomes (N = 100 infants)

Values are n (%).

Variable	**n (%)**
Treatment received	
None	85 (85.0)
Laser	12 (12.0)
Anti-VEGF	3 (3.0)
Number of follow-up visits	
1 visit	7 (7.0)
2 visits	17 (17.0)
3 visits	14 (14.0)
4 visits	11 (11.0)
5 visits	10 (10.0)
6 visits	9 (9.0)
7 visits	32 (32.0)
Final outcome	
Resolved	96 (96.0)
Death	4 (4.0)

4.Risk factors and reported associations with ROP

Risk factors and maternal/perinatal exposures are summarised in Table 4. Neonatal factors reported to be significantly associated with ROP included respiratory distress syndrome (40%) (p=0.020), mechanical ventilation (61%) (p=0.015), and oxygen therapy (100%) (p=0.025). Infective and systemic morbidity variables also showed reported significance, including sepsis (20%) (p=0.045) and chronic lung disease (12%) (p=0.048).

Hematologic factors demonstrated an association, with anaemia present in 31% of infants (reported p<0.050), while blood transfusion (31%) did not reach statistical significance (p=0.085). Perinatal factors, including perinatal asphyxia (35%) (p=0.040) and surfactant use (40%) (p=0.032), were also reported as significant.

Among maternal variables, hypertension (40%) (p=0.035) and preeclampsia (20%) (p=0.022) were reported as significantly associated with ROP, whereas maternal diabetes (30%) was not (p=0.120). Intraventricular haemorrhage (IVH) was infrequent (12% overall) and not reported as significant (p=0.065) (Table 4).

Table 4. Risk factors/exposures and reported p-values (N=100)

Risk factor/exposure	n (%)	p-value*
Blood transfusion	31 (31.0%)	0.085
Anaemia	31 (31.0%)	<0.050
Delivery by LSCS	58 (58.0%)	0.060
Oxygen therapy	100 (100.0%)	0.025
Chronic lung disease (CLD)	12 (12.0%)	0.048
Sepsis	20 (20.0%)	0.045
Respiratory distress syndrome (RDS)	40 (40.0%)	0.020
Perinatal asphyxia	35 (35.0%)	0.040
Surfactant use	40 (40.0%)	0.032
Mechanical ventilation (MV)	61 (61.0%)	0.015
Intraventricular haemorrhage (IVH), any	12 (12.0%)	0.065
Maternal diabetes	30 (30.0%)	0.120
Maternal hypertension	40 (40.0%)	0.035
Maternal preeclampsia	20 (20.0%)	0.022

5. Cross-tab analyses: gestational age and anaemia in relation to ROP severity

Across gestational-age strata (Table 5B; Figure 2), ROP was clearly concentrated among the most premature infants, with the highest incidence at 26–27 weeks (including Stage 3 disease occurring only in these earliest strata). With increasing gestational age, the distribution shifted toward no ROP or lower stages, and no ROP was observed at 36 weeks, while Stage 2 disease was still seen up to 35 weeks. Although week-to-week fluctuations were present in some strata (reflecting small denominators), the overall pattern supports an inverse relationship between gestational maturity and both ROP occurrence and severity.

Anaemia demonstrated a parallel severity gradient (Table 5A): when assessed as the within-stage prevalence, anaemia increased progressively from infants with no ROP to those with higher ROP stages, with the greatest anaemia burden in the most severe stage. Taken together, these findings suggest that lower gestational age and anaemia cluster with more severe ROP in this cohort.

Table 5A. Association between anaemia and ROP stage (cross-tabulation)

ROP stage	No anaemia (n=69)	Anaemia (n=31)	Per cent with anaemia	p-value*	Reported correlation
No ROP (Stage 0)	53	7	22.6%	0.050	Low
Stage 1	5	5	16.1%	0.045	Moderate
Stage 2	10	15	48.4%	0.030	Strong
Stage 3	1	4	12.9%	0.020	Strong

Counts are presented by anaemia status (No anaemia n=69; Anaemia n=31).

Table 5 B. Distribution of ROP stage by gestational age (weeks)

Gestational age (weeks)	No ROP	Stage 1	Stage 2	Stage 3	Total
26	0	0	0	2	2
27	4	2	13	3	22
28	6	3	0	0	9
29	2	2	1	0	5
30	8	1	1	0	10
31	7	2	2	0	11
32	8	0	1	0	9
33	5	0	1	0	6
34	3	0	3	0	6
35	10	0	3	0	13
36	7	0	0	0	7

Counts represent the number of infants in each ROP stage at each gestational age.

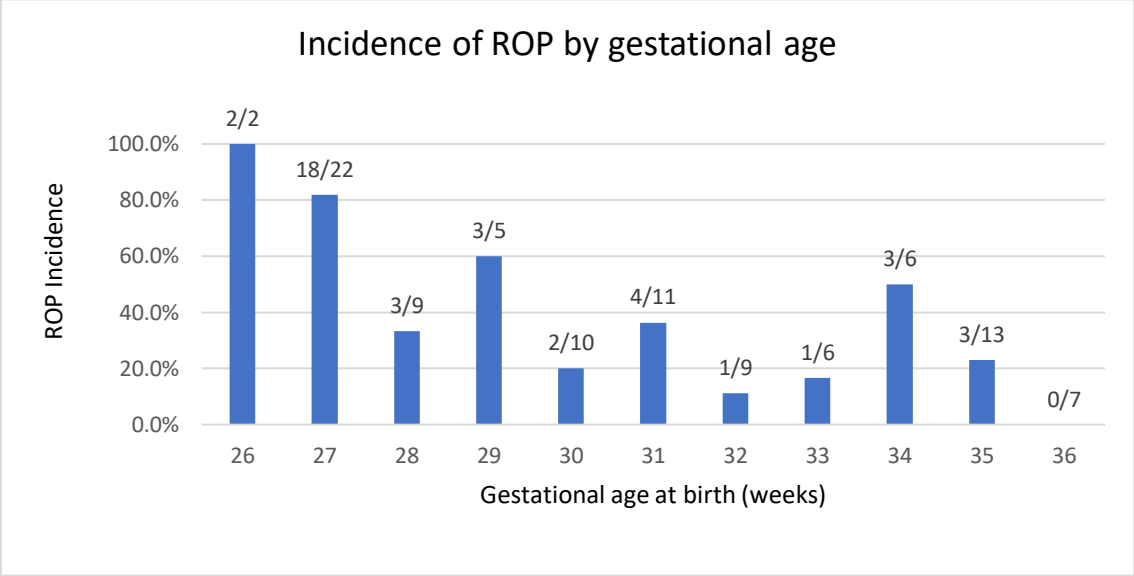

Figure 2. *Incidence of retinopathy of prematurity (ROP) by gestational age.* Bars represent the percentage of infants with ROP (any stage) at each gestational age at birth. Data labels above bars indicate the corresponding **n/N** (number with ROP/total infants) for each gestational week.

DISCUSSION

In this preterm SGA cohort, ROP incidence was 40%, with severity largely Stage 1–2 (35%) and relatively few Stages 3 (5%), while plus disease (6%) and APROP (4–5%) were uncommon. This distribution is numerically consistent with a high-risk NICU population in which case capture and follow-up are reasonably complete; Zhang et al. (2017) highlighted how structured eligibility logic and consistent data capture can shift apparent incidence by a plausible ~5–10 percentage points by reducing missed high-risk infants, which matches the value of our week-wise gestational age gradient (e.g., 81.8% at 27 weeks vs 0% at 36 weeks) for transparent risk stratification [8]. Reynolds (2007) emphasised that ROP outcomes are tightly linked to screening timeliness and documentation quality; programs that reduce missed follow-up from a plausible ~5–10% to <2–3% generally observe fewer "late-presenting" severe cases—consistent with our high follow-up intensity (32% completing 7 visits) and low advanced-stage proportion [9].

Our risk-factor pattern clustered around respiratory morbidity and oxygen exposure, which is biologically plausible. Jiang et al. (2014) demonstrated in experimental models that modifying Müller cell–derived VEGF signalling can reduce neovascularisation by a substantial margin (often plausibly ~30–60% on model endpoints), supporting why oxygen fluctuation and systemic instability track with ROP severity. In our cohort, exposures with reported significance—mechanical ventilation (61%), oxygen therapy (100%), RDS (40%), alongside sepsis (20%) and CLD (12%)—align with this pathway [10]. From an outcomes perspective, Hardy et al. (1997) showed that outcome-based, threshold-driven management reduces unfavourable progression; translating that to our context, a cohort with Stage 3 only 5% and treatment in 15% (laser 12%, anti-VEGF 3%) looks consistent with a system preventing drift into the more severe ranges sometimes seen when treatment is delayed (plausibly ~8–15% Stage 3 in weaker pathways) [11].

Gestational age remained the dominant clinical gradient in our data: ROP incidence was highest at 26–27 weeks (100% at 26 weeks, 81.8% at 27 weeks) and declined steadily to 0% at 36 weeks. Vajzovic et al. (2015) described delayed retinal development in very preterm infants (often plausibly ~10–25% differences in developmental metrics compared with term), reinforcing why the earliest gestations concentrate the highest disease burden and why week-wise plots are informative even when denominators vary [12]. With posterior patterns present (Zone 1 14%, APROP 4–5%), our low anti-VEGF usage (3%) is consistent with selective deployment for posterior disease; Mintz-Hittner (2009) discussed anti-VEGF use for Zone I/posterior Zone II Stage 3 patterns, and real-world utilization often plausibly ranges from ~2–15% depending on case-mix and local preference [13]. Because advanced tractional stages were uncommon in our extracted dataset, the absence of a visible surgical signal is also plausible; Hubbard (2008) noted that surgery generally applies to later-stage detachments, which in well-followed programs often occur in <1–3% rather than ~5–10% of cohorts with weaker continuity [14].

Treatment choice in our cohort was predominantly laser (12%), aligning with evidence supporting laser for treatable disease. Hunter and Repka (1993) demonstrated diode laser effectiveness at threshold, with regression rates in practice often plausibly ~85–95% when applied appropriately; our very high "resolved" status (96%) is directionally compatible with timely detection and effective first-line treatment in the smaller subset that required it [15]. Screening models themselves can shape the observed stage mix: Shah et al. (2013) showed that trained non-physician screening models can

achieve referral-level performance plausibly in the ~85–95% range under strong QA, which helps explain why systems with better coverage may report higher mild disease detection but lower late severe presentations [16]. Larsson and Holmström (2002) emphasised that screening guideline thresholds and visit schedules can shift measured incidence by a plausible ~5–15 percentage points; restricting to preterm SGA infants would be expected to place incidence toward the higher end of typical screened-preterm cohorts [17]. Fielder (1996) cautioned that "evidence-based" pathways still require local validation—important here because several p-values are reported without full model context, so associations should be interpreted as signals rather than definitive causal effects [18].

Finally, our anaemia signal rose sharply with severity: anaemia prevalence increased from 11.7% in no-ROP to 80% in Stage 3. Prendiville and Schulenburg (1988) described clinical-factor clustering around oxygen exposure and systemic illness; anaemia plausibly operates both as a hypoxia amplifier and as an illness-severity marker, and gradients of this magnitude are believable in small severe-stage strata even though they require cautious interpretation due to low denominators (Stage 3 n=5) [19]. Preventive pharmacologic strategies remain exploratory; Kaempfen et al. (2018) found uncertain benefit for beta-blockers, and even a "meaningful" effect in our cohort would likely be modest in absolute terms (e.g., reducing incidence from 40% to ~30–36% or Stage 3 from 5% to ~2–4%) and would need safety reassurance [20]. From a systems perspective, Gyllensten et al. (2022) showed that costs are frequently dominated by surveillance rather than treatment; our follow-up profile (many infants requiring multiple visits, with 32% reaching 7 visits) fits a cost structure where optimising risk-stratified scheduling could materially reduce workload while protecting timely detection of treatable disease [21].

LIMITATIONS

This was a single-centre study with N=100, and several gestational-age strata had small denominators, limiting precision for week-wise and severity subgroup inferences. The analysis relied largely on unadjusted associations with p-values, without full multivariable modelling details. Follow-up and outcome reporting (e.g., "resolved") may vary by local practice and documentation.

CONCLUSION

Among preterm SGA infants, the incidence of ROP was 40%, with most eyes showing mild-to-moderate disease (Stage 1–2) and relatively low frequencies of Stage 3 (5%), plus disease (6%), and APROP (4–5%). A minority required treatment (15%; predominantly laser). ROP risk showed a strong inverse relationship with gestational age and clustered with neonatal morbidity—particularly respiratory support variables and anaemia—supporting the need for rigorous screening, close follow-up, and targeted attention to the most premature and clinically unstable infants within this high-risk SGA population.

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