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Retinopathy of prematurity in preterm infants: A prospective study of prevalence and predictors in Northern India

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ABSTRACT

Objectives: To determine the prevalence and predictors of Retinopathy of prematurity (ROP) and severe ROP.
Methods: A prospective observational study (April 2019–May 2020) was conducted at a tertiary care center in preterm newborns with; 1) birth-weight <2000 g or gestation <34 weeks and 2) gestation 34–36 weeks with risk factors that predispose to ROP.
Results: A total of 340 preterm newborns were screened. ROP was diagnosed in 63 (18.5%), of which 8 (2.4%) had severe ROP. 30.2%, 63.5%, and 9.5% babies had stage 1, 2, and 3 ROP, respectively. Perinatal risk factors for ROP were assessed using univariate analysis. In the binary logistic regression analysis, birth-weight<1250 g, gestation<30 weeks, weight-gain proportion at 4, 5 and 6 weeks, respiratory distress syndrome (RDS), surfactant administration, need for oxygen were significantly associated with ROP while birth-weight<1250 g, apnea, surfactant administration and oxygen duration≥80 h were associated with severe ROP ($p < 0.005$). Infants with poor postnatal weight-gain were found to be at risk for ROP. ROC plot depicted an absolute weight gain of 535 g at 6-weeks of age had a sensitivity of 58.7% and specificity of 32.9% for predicting ROP.
Conclusion: The prevalence of ROP was 18.5%. Birth-weight<1250 g, gestation <30 weeks, weight-gain proportion at 4, 5 and 6 weeks, RDS, surfactant administration, need for oxygen were independent predictors for ROP, however birth-weight<1250 g, apnea, surfactant administration and oxygen duration ≥80 h were independent predictors for severe ROP. Preterm newborns with poor postnatal weight-gain are at risk for ROP.

1. Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the retina that can produce significant vision impairment in infants and remains one of the leading causes of preventable blindness.[1] The incidence of ROP increases with decreasing gestation and birth weight; however, not all preterm newborns develop it.[1] Hence, there ought to be other possible prenatal and postnatal risk factors responsible such as hypoxia, hyperoxia, sepsis, shock, necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), prolonged exposure to oxygen (O2), severity of neonatal illnesses, mechanical ventilation, prolonged ventilatory support, anemia, blood transfusion, acidosis, high ambient light, and vitamin E deficiency, etc.[2,3]

The World Health Organization (WHO) program of Vision 2020 emphasizes the importance of early screening and referral in reducing the incidence of ROP.[4] The world is facing the third epidemic of ROP, emerging as a significant public health concern in low and middle-income countries.[5] Among them, India contributes to nearly 10% of the worldwide estimate of blindness and visual impairment due to ROP.[5] Great disparities in the quality of neonatal care among peripheral and tertiary care centers, along with increased survival of preterm neonates, are significant reasons. This coupled with low coverage of screening and management services due to a lack of awareness of ROP among healthcare workers, parents, and counselors along with the scarcity of trained ophthalmologists and neonatologists in the community, intensifies the problem. It has been observed that the majority of babies in these countries present with stage five disease and are heavy and more mature. Thus, it seems logical that the screening guidelines for ROP in developing countries should include simple, easily identifiable risk factors which could help in the early identification of at-risk newborns and possibly prevent sight-threatening ROP. Hence, we conceived this study to determine the prevalence of ROP and severe ROP and analyze the predictors for its development.

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Abbreviations

ROP	Retinopathy of Prematurity
NEC	Necrotizing Enterocolitis
IVH	Intra Ventricular Haemorrhage
WHO	World Health Organization
CPAP	continuous positive airway pressure
RDS	respiratory distress syndrome
PDA	Patent Ductus Arteriosus
HDN	Haemorrhagic Disease of Newborns
SPO2	oxygen saturation
FiO2	fraction of inspired oxygen
PIH	Pregnancy Induced Hypertension
APH	antepartum haemorrhage
MSAF	meconium stained amniotic fluid
ACS	antenatal corticosteroid administration
AAP	American Academy of Pediatrics
NNF	National Neonatology Forum
ICROP	International Classification of ROP
ETROP	Early Treatment for Retinopathy of Prematurity Randomized Trial
ROC	Receiver operating characteristic
BW	Birth Weight
GA	Gestation Age
OR	Odds Ratio
PA	Perinatal Asphyxia
VEGF	Vascular endothelial growth factor
NNH	Neonatal Hyperbilirubinemia
SA	Surfactant administration
ET	Exchange Transfusion

2. Patients and methods

This prospective observational study was conducted at a tertiary care center in Northern India comprising of both inborn and outborn newborns between April 2019 and May 2020. The study was approved by Institutional ethical committee. All admitted newborns were screened for the study. The inclusion criteria's were: 1) preterm newborns with birth weight <2000 gm or gestational age <34 weeks; 2) selected preterm newborns between 34 and 36 weeks gestational age with any of the following: continuous positive airway pressure (CPAP) or ventilation for any duration, oxygen therapy for ≥24 h, vasopressors support, blood transfusion and culture positive sepsis. Exclusion criteria's were: preterm newborns with major congenital anomalies and where parents declined enrolment and follow-up. The eligible preterm newborns were recruited after written consent from either of the parents. All neonatal and maternal details were recorded in a predesigned proforma.

Neonatal details like gestational age (GA), birth weight (BW), gender, apneic episodes, type of oxygen supplementation and duration, blood transfusion, hyperbilirubinemia, exchange transfusion, hypothermia, sepsis, shock, perinatal asphyxia, seizures, surfactant administration, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and haemorrhagic disease of newborns (HDN) were recorded. GA was determined by antenatal ultrasound in the first trimester or calendar method and confirmed by the New Ballard Score after delivery.[6] Electronic infant weighing scale was used to measure the BW. Postnatal weight gain proportion (%) in the first six weeks of life (4, 5 and 6 weeks) was calculated by: Postnatal weight gain proportion (%) = {[Weight at (x) weeks–BW] ÷ BW} × 100.[7] Perinatal asphyxia was defined as an Apgar score at 1 min<6.[7] Apnoea was identified as cessation of respiration for >20 s/any duration if accompanied by bradycardia or cyanosis.[8] The duration of oxygen administration was recorded and extreme caution was taken to maintain oxygen saturation (SpO2) between 90 and 94% by titrating the fraction of inspired oxygen (FiO2) between 30 and 100%. Preterm newborns with mild to moderate respiratory distress were managed with CPAP and surfactant was administered if symptoms, signs and radiological features were compatible with RDS. Babies failing CPAP were managed with mechanical ventilation. Lung protective strategies were followed and ventilator parameters including FiO2 were noted.

Neonatal sepsis was diagnosed based on clinical suspicion, sepsis screen and microbiological confirmation.[9] Shock was considered by evidence of poor perfusion with tachycardia, cold extremities and capillary refill time >3 s or blood pressure below 5th percentile for GA. Cranial ultrasound was carried out in the first and fourth week as per unit protocol. Echocardiogram was done if the neonate was found to have significant murmur or clinical suspicion for PDA. Anemia was defined as haematocrit or haemoglobin level >2 standard deviations below the mean value for the age.[10] Standard guidelines were followed for blood and exchange transfusion.

Maternal factors like GA, parity, type of delivery, multiple pregnancy, pregnancy induced hypertension (PIH), antepartum haemorrhage (APH), chorioamnionitis, meconium stained amniotic fluid (MSAF) and antenatal corticosteroid administration (ACS) were recorded.

All enrolled preterm newborns were screened for ROP as per the American Academy of Pediatrics (AAP) and National Neonatology Forum (NNF) guidelines.[11,12] Screening of ROP was performed by an ophthalmologist using Retcam Shuttle (Clarity MSI, USA). Pre-treatment of the eyes with a topical Proparacaine was done to minimize discomfort to the babies followed by pupillary dilatation with phenylephrine 2.5% and Tropicamide 0.5%. The universally accepted Revised International Classification of ROP (ICROP) guidelines were adopted to define the location and extent of disease within the retina.[13] The cases were classified on the basis of vascularisation of retina and characterized by its position (zone), severity (stage), and extent (clock hours).

First ROP screening was done at 4 weeks after birth. However, for those <28 weeks GA or BW < 1200 g, screening was done at 2 weeks after birth. Thereafter, they were screened every 2 weeks/earlier until complete vascularisation of retina. The occurrence of ROP changes in either eye was recorded according to ICROP. The preterm newborns were then divided into two groups based on the presence or absence of ROP, Group 1: ROP and Group 2: Non- ROP group. The ROP group was further subdivided into Non-severe ROP (not requiring treatment, comprising of stages 1, 2, and 3 < threshold disease) and severe ROP group (requiring treatment, comprising of threshold ROP, stages 4 and 5). Threshold ROP included ROP of more than five contiguous or eight cumulative clock hours of stage 3 with plus in zone 1 or zone 2. The decision for the treatment of ROP was based on the type of ROP as per Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP).[14] Babies with threshold ROP were treated with laser photocoagulation within 72 h of diagnosis. Additionally, all enrolled preterm newborns were followed at 4, 5, and 6 weeks to observe their weight gain and its impact on the development of ROP. The primary outcome measured was the prevalence of ROP and severe ROP. Secondary outcomes measured were the predictors and outcomes of ROP.

2.1. Statistical analysis

The incidence of ROP in the preterm population was found to be 32.6% and 21.6% in the studies done by Ahuja and Rao et al., respectively.[15,16] Considering the incidence of ROP as 30% with an absolute precision of 5% and confidence level (1-α) 95%, a total of 323 neonates were needed for screening. Continuous variables were analyzed by

student t-test (normally distributed) and Mann-Whitney *U* test (non--normally distributed). Categorical variables were analyzed by Chi -square or Fischer -Exact test. A univariate and binary logistic regression analysis was performed to determine the predictors for ROP and severe ROP. The receiver operating characteristic (ROC) curve was plotted to determine the discriminative cut-off values of postnatal weight gain proportion. Analysis was done using SPSS software 23-version, and a p-value of <0.05 was taken as significant.

3. Results

Of the total 2367 admissions to Neonatal Unit, 412 preterm newborns (17.4%) fulfilled the inclusion criteria. A total of 340 preterm newborns (male, n = 185) were analyzed. ROP (any stage/zone) was detected in (n = 63, 18.5%), and the rest (n = 277) did not have ROP (non-ROP group). Among the ROP group, 55 had non-severe, and 8 had severe ROP; their baseline comparison is shown in Table 1. The mean BW of the ROP and the non-ROP group was 1396.03 ± 260.96 g and 1592.02 ± 196.52 g, respectively, and the mean GA was 30.1 ± 2.1 weeks and 32.4 ± 0.8 weeks respectively, both being significantly less in ROP group (p < 0.001).

A zone and stage-wise distribution of ROP is shown in Fig. 1. Zone I was detected among the infants with ROP in 4.5% (3/63), zone II in 50.8% (32/63), and zone III in 47.6% (30/63). Infants with ROP were: stage 1 in 30% (19/63), stage 2 in 63.5% (40/63), and stage 3 in 9.5% (6/63). The majority of our patients had Zone II involvement and 4.76% developed severe ROP. None of the preterm infants developed stage 4/5.

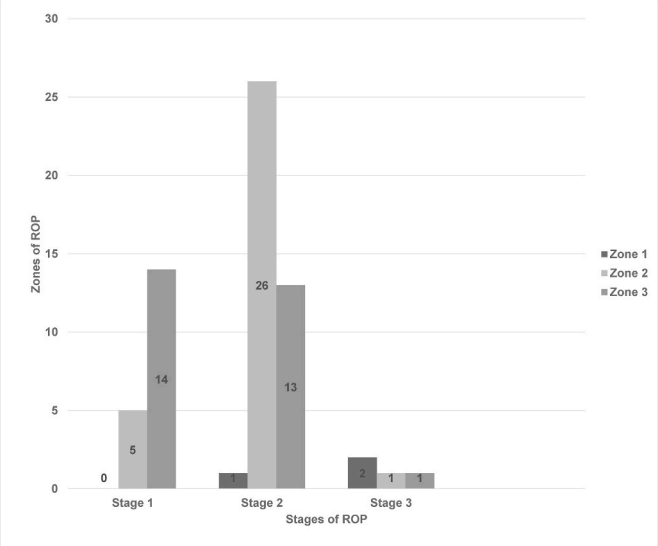

Fig. 1. Stages and zones of ROP (n = 63).

Table 1
Baseline comparisons of parameters among ROP and non-ROP group.

Parameters	ROP Group (n = 63)	Non-ROP Group (n = 277)	p-value
Gender, Male	41 (65.0%)	144 (51.9%)	0.06
Birth Weight (mean ± SD), grams	1396.03 ± 260.96	1592.02 ± 196.52	<0.001
Gestation (mean ± SD), weeks	30.1 ± 2.1	32.4 ± 0.8	<0.001
Postnatal weight gain proportion (mean ± SD)			
1 Weight gain proportion at 4-week	12.45 ± 5.45	15.35 ± 3.33	<0.001
2 Weight gain proportion at 5-week	23.30 ± 12.40	29.17 ± 7.87	<0.001
3 Weight gain proportion at 6-week	33.35 ± 10.24	38.75 ± 6.63	<0.001
Birth weight (grams)			
1 .<1000	5 (7.9%)	0 (0%)	0.05
2. 1000-1249	16 (25.4%)	8 (2.9%)	0.18
3. 1250-1499	22 (34.9%)	108 (38.9%)	<0.001
4. ≥1500	20 (31.8%)	159 (58.2%)	<0.001
Maternal risk factors			
1 Pregnancy induced hypertension	11 (17.5%)	61 (22.0%)	0.42
2 Antepartum haemorrhage	4 (6.3%)	42 (15.2%)	0.07
3 Antenatal corticosteroid administration	9 (14.3%)	43 (15.5%)	0.80
4 Meconium stained liquor	12 (19.0%)	55 (19.6%)	0.88
5 Chorioamnionitis	46 (73.0%)	117 (42.2%)	<0.001
Neonatal risk factors			
1 Respiratory distress syndrome	39 (61.9%)	65 (23.5%)	<0.001
2 Clinical sepsis	46 (73.0%)	117 (42.2%)	<0.001
3 Culture positive sepsis	25 (39.7%)	84 (30.3%)	0.15
4 Perinatal Asphyxia	18 (28.6%)	26 (9.4%)	<0.001
5. Hypotension	9 (14.3%)	34 (12.2%)	0.66
6. Apnea	13 (20.6%)	161 (58.1%)	0.15
7. Blood transfusion	20 (31.7%)	70 (25.2%)	0.29
8. Neonatal hyperbilirubinemia	39 (61.9%)	144 (51.9%)	0.15
9. Surfactant Administration	9 (14.1%)	75 (27%)	0.01
10. Patent ductus arteriosus	5 (7.9%)	14 (5.1%)	0.36
11. Intraventricular haemorrhage	5 (7.9%)	20 (7.2%)	0.84
12. Necrotising enterocolitis	0 (0%)	11 (3.9%)	0.11
13. Haemorrhagic disease of newborn	3 (4.8%)	21 (7.6%)	0.43
14. Exchange transfusion	3 (4.8%)	6 (2.2%)	0.25
Need for oxygen administration	41 (65.1%)	65 (23.5%)	<0.001
Duration of oxygen (hours)	51.2 ± 50.9	12.7 ± 28.5	<0.001
Days of establishment of full enteral feed (days) (mean ± SD)	5.36 ± 2.62	3.17 ± 1.33	<0.001

Values are expressed in number (percentage), and mean (standard deviation).
ROP: Retinopathy of Prematurity, SD: standard deviation.

Table 1 shows the baseline analysis of prenatal and postnatal risk factors between the ROP and non-ROP groups. The prevalence of ROP was higher with a decrease in BW and GA. Apart from these, maternal chorioamnionitis, RDS, clinical sepsis, perinatal asphyxia, surfactant administration, need for oxygen and longer oxygen duration and delayed achievement to full enteral feed were significantly higher in the ROP group. The association of postnatal weight gain proportion in neonates among ROP and the non-ROP group was analyzed at 4, 5, and 6 weeks and was significantly less in the ROP group (p < 0.001). Full enteral feeding was established earlier in the non-ROP group (3 days vs. 5 days, p < 0.001). The oxygen administration [by any mode: hood, nasal prongs, bubble CPAP, or mechanical ventilation] was more often in preterm newborns with ROP (65% vs. 23%; p < 0.001). Similarly, the duration of oxygen administration was longer among ROP (51.2 ± 50.9 vs. 12.7 ± 28.5 h, p < 0.001).

To predict the risk factors for the development of ROP and severe ROP in the preterm newborns, we used variables one by one in univariate analysis and found 11 factors (BW, GA, weight gain proportion at 4, 5, 6 weeks, need for oxygen and longer oxygen duration, RDS, surfactant administration, clinical sepsis, perinatal asphyxia, delayed achievement to full enteral feed, history of chorioamnionitis in mother) to be significantly associated with ROP; however only seven risk factors were significantly associated with the development of severe ROP (BW, GA, perinatal asphyxia, RDS, apnea, need of surfactant and prolonged use of oxygen).

The factors found to be significant in univariate analysis were applied to binary logistic regression analysis (Table 2). Five independent risk factors (BW < 1250 g, GA<30 weeks, weight gain proportion at 4, 5, 6 weeks, RDS, surfactant administration, and need for oxygen.) were found for the development of ROP, while only four (BW < 1250 g, apnea, surfactant administration and oxygen duration ≥80 h) independent risk factors for severe ROP (Table 2).

The present study showed that early postnatal weight gain in preterm neonates has been protective for ROP; hence we analyzed the predictive power of weight gain proportion at 6 weeks for ROP by plotting the ROC (Fig. 2). The area under the curve was only 0.6944 (95% CI: 0.61 to 0.77). The discriminatory power was modest. The absolute weight gain of 535 gms from birth to 6 weeks of age had a sensitivity of 58.7% and

Table 2
Binary logistic regression analysis to determine independent predictors for development of ROP and severe ROP.

Parameters	ROP		Severe ROP	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value
Birth weight <1250 g	12.6 (2.1–73.8)	0.01	102 (4.1–2521)	0.01
Gestation <30 weeks	44.10 (13.8–140.5)	<0.001	55.2 (28.8–87.8)	0.99
Weight gain proportion at 4 weeks ≥ 14	1.10 (1.0–1.7)	0.02	0.14 (0.0–1.2)	0.08
Weight gain proportion at 5 weeks ≥ 24	2.49 (1.1–5.7)	0.01	2.26 (0.2–19.8)	0.46
Weight gain proportion at 6 weeks ≥ 35	6.73 (1.3–33.4)	0.02	1.89 (0.2–16.2)	0.56
Chorioamnionitis	0.99 (0.1–7.9)	0.99	2.2 (0.5–18.9)	0.99
Respiratory distress syndrome	25.56 (1.28–65.81)	0.04	12.5 (2.4–67.9)	0.99
Blood transfusion	1.1 (0.2–23.5)	0.54	0.18 (0.0–1.1)	0.06
Apnea	2.1 (0.1–26.5)	0.24	3.3 (1.4–7.8)	0.01
Surfactant administration	0.20 (0.1–0.8)	0.02	0.05 (0.0–0.6)	0.01
Perinatal asphyxia	0.89 (0.2–3.5)	0.88	0.25 (0.0–2.0)	0.19
Sepsis	4.44 (0.5–38.2)	0.17	7.6 (0.9–84.7)	0.99
Oxygen needed	31.77 (1.8–561.9)	0.02	16.7 (2.1–88.2)	0.99
Oxygen duration ≥80 h	0.23 (0.1–1.0)	0.05	4.7 (2.1–16.3)	0.01
Day to full enteral feed ≥4 days	2.78 (0.7–10.5)	0.13	1.95 (0.3–13.9)	0.50

ROP: Retinopathy of Prematurity, OR: Odds Ratio, CI: Confidence interval.

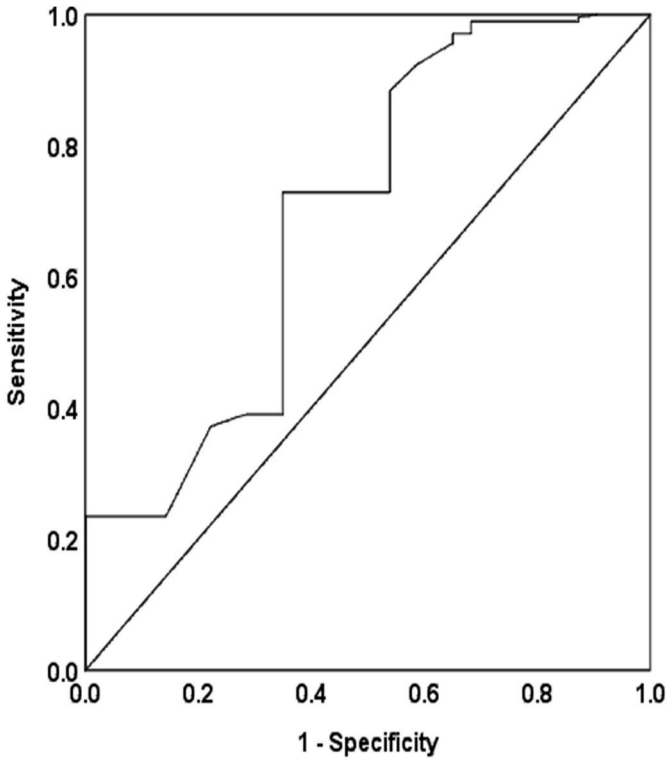

Fig. 2. ROC curve for postnatal weight gain at 6 weeks and development of ROP.

specificity of 32.9% for predicting ROP. The severe ROP cohort (n = 8) was treated with laser ablation (n = 5) and anti-vascular endothelial growth factor (VEGF) (n = 3). All of them had regression following treatment.

4. Discussion

ROP has been reported in India for 21.7%–51.9% of low birth weight infants.[17–22] In our study, the prevalence of ROP and severe ROP was 19.1% and 2.47%, respectively. This was similar to studies done by Rao et al. [16] and Maheshwari et al.[23] with the inclusion of neonates with GA ≤35 weeks and BW ≤ 1500 g, which was 20%. The slight differences among the incidences of ROP in various studies may be related to different cut-offs of BW and GA, genetics profile, level of neonatal care, and methodology of research.[24,25] In our study, univariate analysis showed a significant relationship between the incidence of ROP (Any ROP and severe ROP) and lower BW and GA. Both have been identified as the main risk factors for the incidence of ROP by numerous studies.[23–25] BW ≤ 1250 g and GA≤30 weeks were also found to be an independent risk factors for development of ROP.

Among the prenatal risk factors, APH, PIH, ACS, MSAF, and chorioamnionitis have been found to be significantly associated with ROP; though we only found chorioamnionitis as a risk factor here.[26–28] Neonatal clinical sepsis was also found to be a risk factor on univariate analysis, and 73% of the ROP group had clinical sepsis (p < 0.001), which corroborates with findings of other studies.[29–31] Gupta et al. reported 52% sepsis among babies with ROP and observed that the risk of ROP was independently proportional to the presence of bacterial and fungal sepsis only in ELBW babies and those with threshold ROP.[29] Both, maternal chorioamnionitis and neonatal sepsis have been reported as a risk factor for ROP in other study.[32] The probable explanation for both seems to be hemodynamic instability caused by sepsis leading to hypotension and fluctuation of oxygen saturation which in turn causes alteration in retinal perfusion resulting in retinal ischemia and poor perfusion. Another possible elucidation could be that the increased systemic pro-inflammatory cytokines exert a direct effect on retinal neovascularization via VEGF production. Thus, it can be assumed that early prevention and treatment of sepsis may help in reducing the risk of ROP. A study by Rosemary et al. also showed a protective effect of maternal antenatal steroid administration on the development of ROP in neonates, which was not seen in the present study.[26]

We also observed that perinatal asphyxia was an essential determinant for ROP; akin to Shah et al., who observed a higher risk of ROP in preterm babies with lower APGARs at 1 min.[33] RDS was also found to be a significant risk factor in the present study and an independent risk factor on binary logistic regression analysis for the development of ROP, similar to the study done by Gupta et al., who observed ROP in 33.3% with RDS.[29] In our study, 61.9% of babies in the ROP group had RDS, which is comparable to existing literature.[15,16] Surfactant administration has also been shown to be protective for ROP, and we observed the same in the present study(p = 0.01).[15,16] A valid rationale is that these neonates eventually had lesser oxygen requirement and exposure. The preterm lungs are immature and are usually exposed to prolonged oxygen, often at high concentrations. Animal studies have demonstrated that immature retina is susceptible to such high concentrations of oxygen, which leads to vasoconstriction of these immature vessels. This vasoconstriction initiates continuous retinal tissue hypoxia even after discontinuation of oxygen, leading to the up regulation of VEGF.[34] VEGF, in turn, can stimulate retinal angiogenesis and plays a vital role in the pathogenesis of ROP. Moreover, some studies have reported that significant changes in blood oxygen saturation resulting from apnea and oxygen therapy can also predispose to ROP through the above mechanism.[35]

Prolonged parenteral nutrition is a risk factor for ROP, as concluded in the study by Porcelli et al.[36] Likewise, in our study ROP group had a late establishment of enteral feeds compared to non-ROP; however it

was not found to be an independent risk factor for ROP. The need for oxygen and delayed achievement to full enteral was significantly associated with ROP compared to the non-ROP group. These findings were in accordance with Sathar et al.[37]

In our study, parameters like BW < 1250 gms, apnea, surfactant not used, and longer oxygen duration ≥80 h were found to be independent predictors for the development of severe ROP. This reflects that patients requiring oxygen are more prone to severe respiratory disease, thus, are more likely to have fluctuations in oxygen concentration and episodes of hypoxia and hyperoxia that might exaggerate the risk of developing ROP.[38]

We also observed that the weight gain proportion at 4, 5, and 6 weeks was significantly less in the ROP group as compared to the non-ROP group. It suggests that poor postnatal weight gain is associated with a higher incidence of ROP. This has been demonstrated as a risk factor in a few studies (Kamath et al.[39]; Binenbaum et al.[40]). It may be a direct consequence of the early establishment of feeding and can play an important role in preventing/predicting ROP. This observation can be largely applied to community ROP screening programs in developing countries where the importance of early initiation of feeding is essentially ignored.

The present study highlights the magnitude of the problem due to ROP in our preterm population. The incidence is likely to increase as smaller babies survive unless a parallel reduction in other risk factors occurs.

We have looked for an association between weight gain proportion and ROP, which is a novel concept. Further cut-off values can be estimated, which can help better identify newborns at risk and early referral. The use of simple observations like weight gain proportion and time to establish full enteral feeds, which can be easily picked up at the community level, may be incorporated in the National guidelines of developing countries to facilitate early referrals of preterm neonates at risk of ROP.

Our study was powered by its prospective nature and rigorous protocols. We considered many maternal and neonatal risk factors for predicting ROP; however, there are a few limitations, like being a single-center study with a small sample size and fewer patients in the severe ROP group. Also, factors such as fluctuations in oxygen saturation were not measured which plays an important role in pathogenesis of ROP. Our study was conducted at a tertiary care referral center where sick babies are in the majority, so our results cannot be generalized for all preterm infants.

5. Conclusion

Low birth weight and prematurity were the most important predictors for developing any ROP. At the same time, respiratory distress syndrome, surfactant administration, and the need for oxygen were independent predictors for any ROP. Birth weight<1250 gm, apnea, surfactant administration, and oxygen duration≥80 h were independent predictors for severe ROP. Poor postnatal weight gain at 4, 5, and 6 was independently associated with developing ROP.

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Ethics statement

The study was conducted after taking approval from the institutional human ethics committee. Informed written consent was taken from the study participants.

Declaration of competing interest

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1 Isenberg SJ, Eye disorders, MacDonald MG, Mullet MD, Seshia MMK, Avery's Neonatology-Pathophysiology and Management of the Newborn. sixth ed, Philadelphia, PA, Lippincott Williams and Wilkins, 1469-1484.
2 Vanderveen DK, Zupancic JAF. Retinopathy of prematurity. In: Cloherty JP, Eichenwald EC, Stark AR, eds. *Manual of Neonatal Care*. sixth ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2010:640–644.
3 Singh M. Miscellaneous conditions: retinopathy of prematurity. In: *Care of the Newborn*. seventh ed. New Delhi: Sagar Publications; 2010:425–428.
4 Gilbert C, Foster A. Childhood blindness in the context of vision 2020- the right to sight. *WHO Bulletin*. 2001;79:227–232.
5 Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. *Lancet*. 1997;350(9070):12–14.
6 Ballard JL, Khoury JC, Wedig KL, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. *J Pediatr*. 1991;119: 417–423.
7 Sivanandan S, Chandra P, Deorari AK, Agarwal R. Retinopathy of prematurity: AIIMS, New Delhi experience. *Indian Pediatr*. 2016;53(suppl 2). S123–8.
8 Stark AR. Apnea. In: Cloherty JP, Eichenwald EC, Stark AR, eds. *Manual of Neonatal Care*. seventh ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012:397–406.
9 Puopolo KM. Bacterial and fungal infections. In: Cloherty JP, Eichenwald EC, Stark AR, eds. *Manual of Neonatal Care*. seventh ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2010:274–300.
10 Christou HA. Anemia. In: Cloherty JP, Eichenwald EC, Stark AR, eds. *Manual of Neonatal Care*. seventh ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2010: 563–571.
11 Fierson WM. American Academy of Pediatrics Section on Ophthalmology; American academy of ophthalmology; American association for pediatric ophthalmology and strabismus; American association of certified orthoptists. Screening Examination of Premature Infants for Retinopathy of Prematurity [published correction appears in Pediatrics, 2019 Mar;143(3):] *Pediatrics*. 2018;142(6), e20183061.
12 National neonatology forum, Screening and Management of Retinopathy of Prematurity 2020, p231-p236.
13 Committee for the classification of retinopathy of prematurity: an international classification of retinopathy of prematurity. *Arch Ophthalmol*. 1984;102:1130–1134.
14 Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003; 121(12):1684–1694.
15 Ahuja AA, Reddy YC, Adenuga OO, Kewlani D, Ravindran M, Ramakrishnan R. Risk factors for retinopathy of prematurity in a district in South India: a prospective cohort study. *Oman J Ophthalmol*. 2018;11:33.
16 Rao KA, Purkayastha J, Hazarika M, Chaitra R, Adith KM. Analysis of prenatal and postnatal risk factors of retinopathy of prematurity in a tertiary care hospital in South India. *Indian J Ophthalmol*. 2013;61:640.
17 Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. *Indian J Ophthalmol*. 1995;43:123–126.
18 Gopal L, Sharma T, Ramchandran S. Retinopathy of prematurity: a study. *Indian J Ophthalmol*. 1995;43:59–61.
19 Jalali S, Matalia J, Hussain A, Anand R. Modification of screening criteria for retinopathy of prematurity in India and other middle-income countries. *Am J Ophthalmol*. 2006;141:966–968.
20 Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care centre—incidence, risk factors and outcome. *Indian Pediatr*. 2009;46:219–224.
21 Hungi B, Vinekar A, Datti N, et al. Retinopathy of Prematurity in a rural neonatal intensive care unit in South India-a prospective study. *Indian J Pediatr*. 2012;79: 911–915.
22 Varughese S, Jain S, Gupta N, Singh S, Tyagi V, Puliyel JM. Magnitude of the problem of retinopathy of prematurity, experience in a large maternity unit with a medium size level-3 nursery. *Indian J Ophthalmol*. 2001;49:187–188.
23 Maheshwari R, Kumar H, Paul VK. Incidence and risk factors of retinopathy of prematurity in a tertiary care new born unit in New Delhi. *Natl Med J India*. 1996;9: 211–214.
24 Lee S, Charles BA, Millan Ohlesson, Christopher Vincu M. Evidence for changing guidelines for routine screening for retinopathy of prematurity. *Arch Pediatr Adolesc Med*. 2001;155(3):387–395.
25 Donahue SP. Retinopathy of prematurity. *Br J Ophthalmol*. 2002;86:1071–1074.
26 Higgins RD, Mendelsohn AL, DeFeo MJ, Ucsel R, Hendricks-Munoz KD. Antenatal dexamethasone and decreased severity of ROP. *Arch Ophthalmol*. 1998;116:601–605.
27 Moise AA, Wearden ME, Kozinetz CA, Gest AL, Welty SE, Hansen TN. Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. *Pediatrics*. 1995;95:845–850.

28 Horbar J. Antenatal corticosteroid treatment and neonatal outcomes for infants 501-1500 grams in the Vermont-Oxford Trials Network. *Am J Obstet Gynecol*. 1995;173:275–281. for the investigators of the Vermont-Oxford Trials Network.

29 Gupta VP, Dhaliwal U, Sharma R, Gupta P, Rohatgi J. Retinopathy of prematurity – risk factors. *Indian J Pediatr*. 2004;71:887–892.

30 Gunn TR, Easdown J, Outerbridge EW. Risk factors in retrolental fibroplasia. *Pediatrics*. 1980;65:1096.

31 Agarwal R, Deorari AK, Azad RV, et al. Changing profile of retinopathy of prematurity. *J Trop Paediatr*. 2002;48:239–242.

32 Dammann O, Maria-Jantje B, Bartels DB, et al. Immaturity, perinatal inflammation, and retinopathy of prematurity: a multi-hit hypothesis. *Early Hum Dev*. 2009;85:325–329.

33 Shah VA, Yeo CL, Ling YLF, Ho LY. Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore. *Ann Acad Med Singapore*. 2005;34:169–178.

34 Pierce EA, Foley ED, Smith LE. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. *Arch Ophthalmol*. 1996;114, 12190-28.

35 Shohat M, Reisner SH, Krikler R, Nissenkorn I, Yassur Y, Ben-Sira I. Retinopathy of prematurity: incidence and risk factors. *Pediatrics*. 1983;72:159–163.

36 Porcelli PJ, Weaver Jr RG. The influence of early postnatal nutrition on retinopathy of prematurity in extremely low birth weight infants. *Early Hum Dev*. 2010;86:391–396.

37 Sathar A, Shanavas A, Girijadevi PS, Jasmin LB, Kumar SS, Pillai RK. Risk factors of retinopathy of prematurity in a tertiary care hospital in South India. *Clin Epidemiology Glob Health*. 2018;6:44–49.

38 Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr*. 2010;157:69–73.

39 Kamath KM, Asha MN, Vinay V. Correlation between postnatal weight gain and development of retinopathy of prematurity: an experience in rural tertiary care centre. *J Clin Diagn Res*. 2019;13:SC01–SC04.

40 Binenbaum G, Ying GS, Quinn GE, Dreiseitl S, Karp K, Roberts RS. A clinical prediction model to stratify retinopathy of prematurity risk using postnatal weight gain. *Pediatrics*. 2011;127:e607–e614.