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Original Research Article

A Study to Find the Correlation of Fetal Hemoglobin Level and Grade of Retinopathy of Prematurity in Preterm Infants

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Conflict of interest: Nil

Abstract:

Background: Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder of preterm infants and an important preventable cause of childhood visual impairment. Its development is multifactorial and is influenced by gestational age, birth weight, oxygen exposure, sepsis, respiratory morbidity, blood transfusion, and other neonatal factors. Fetal hemoglobin (HbF), because of its higher oxygen affinity compared with adult hemoglobin, may influence retinal oxygen delivery and therefore potentially modify ROP development and severity.

Aim: To evaluate the relationship between fetal hemoglobin levels and the severity of retinopathy of prematurity in preterm infants and to determine whether serial HbF monitoring may have value in ROP risk assessment.

Methods: A prospective longitudinal observational study was conducted in the ROP Clinic and Neonatal Intensive Care Unit of S.C.B. Medical College and Hospital, Cuttack, Odisha, from January 2024 to December 2025. One hundred preterm infants fulfilling the study eligibility criteria were enrolled. Infants with birth weight ≤1500 g or those weighing ≤2000 g with additional ROP-associated risk factors were included. HbF was estimated at birth and weekly for six weeks using high-performance liquid chromatography. ROP screening was performed by indirect ophthalmoscopy and graded according to the International Classification of Retinopathy of Prematurity. Demographic, perinatal, hematological, respiratory, infectious, transfusion, and ophthalmic variables were recorded. Statistical analysis was performed using JAMOVI version 2.6.44.

Results: The study population had a mean gestational age of 30.6±2.47 weeks, ranging from 26 to 34 weeks, and a mean birth weight of 1300±294 g, ranging from 808 to 1782 g. Sepsis was present in 50% of infants, respiratory distress syndrome in 58%, blood transfusion was required in 48%, and hyperbilirubinemia occurred in 49%. Mean HbF showed a progressive decline from 77.9% at birth to 65.9% at six weeks. The longitudinal reduction in HbF was highly significant ($F=376.978$, $p<0.001$). However, the interaction between time and ROP grade was not statistically significant ($F=0.276$, $p=1.000$), and the between-subject effect of ROP grade on HbF was also not significant ($F=0.433$, $p=0.785$). Thus, HbF declined progressively with postnatal age, but the magnitude of decline did not differ significantly according to ROP grade.

Conclusion: HbF demonstrates a marked and consistent postnatal decline in preterm infants during the first six weeks of life. However, in this cohort, HbF decline was not independently associated with the severity of ROP. HbF appears more likely to be a physiological and potentially modifying factor within the multifactorial pathogenesis of ROP rather than an isolated determinant of disease grade.

Keywords: Fetal Hemoglobin; HbF; Retinopathy of Prematurity; Preterm Infants; Retinal Vascularization; Neonatal Anemia.

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Introduction

Due to insufficient retinal vascularization before birth, preterm children are more likely to develop retinopathy of prematurity (ROP), a vasoproliferative condition of the developing retina. The peripheral retina becomes avascular and susceptible to postnatal changes in oxygenation when normal vascular development is prematurely interrupted. Fibrovascular proliferation, retinal detachment, and irreversible vision loss may result from hypoxia-driven pathological

neovascularisation that follows delayed physiological vascular growth caused by subsequent variations in oxygen tension. ROP is still a significant contributor to avoidable childhood blindness, especially in low- and middle-income nations where the population at risk has increased due to rising neonatal survival. ROP is complex in both its development and severity. While sepsis, respiratory distress syndrome, prolonged oxygen therapy, mechanical ventilation, blood transfusions, hyperbilirubinemia, and other systemic complications may also affect retinal vascular development, lower gestational age and birth weight continue to be the best known predictors. Because severe illness may occur at comparatively higher gestational ages and birth weights than generally recognised, ROP is particularly significant in India [1].

This highlights the need for enhanced risk stratification beyond conventional screening metrics. There may be a significant physiological connection between foetal haemoglobin and retinal oxygenation. Compared to adult haemoglobin (HbA), HbF has a higher affinity for oxygen and is more prevalent at birth in preterm neonates. This feature reduces oxygen unloading to tissues while facilitating placental oxygen delivery. The oxygen dissociation properties of circulating blood are altered after premature delivery when HbF is gradually replaced by HbA. Because transfused red blood cells mostly contain HbA, blood transfusions can hasten this change even more. Enhanced oxidative stress and aberrant retinal angiogenesis may result from increased oxygen delivery to the developing retina. Lower HbF fractions may be linked to a higher incidence or severity of ROP, according to earlier research [2].

Nevertheless, there is still a dearth of evidence, and the results are not totally consistent. Gestational age, anaemia, sepsis, transfusion exposure, oxygen therapy, and postnatal maturation are significant complicating variables. As a result, the dynamic haematological changes that take place during the crucial stage of retinal vascular formation may not be sufficiently reflected by a single HbF test. A more insightful evaluation of the connection between HbF kinetics and ROP may be possible through serial monitoring in the early postnatal weeks. In order to assess serial HbF levels from birth to the first six weeks of life and ascertain their correlation with ROP grade in preterm newborns, the current study was created. Major clinical risk variables such as gestational age, birth weight, sepsis, respiratory distress syndrome, blood transfusion, and hyperbilirubinemia were also taken into account [3].

Aim: To evaluate the relationship between fetal hemoglobin (HbF) levels and the severity of retinopathy of prematurity (ROP) in preterm infants and to determine whether serial HbF monitoring can aid in early prediction and risk stratification of ROP.

Objectives

Primary objective: To determine the correlation between fetal hemoglobin levels and the grade of retinopathy of prematurity in preterm infants undergoing routine ROP screening.

Secondary objectives:

1. To assess the weekly trend of HbF levels during the first six weeks of life and its association with the development or progression of ROP.
2. To evaluate whether HbF estimation can serve as an adjunctive risk indicator for early identification of infants at high risk of severe ROP.
3. To analyze the relationship between HbF levels and clinical risk factors for ROP, including gestational age, birth weight, sepsis, respiratory distress, blood transfusion, and hyperbilirubinemia.

Materials and Methods

Study Design: This was a prospective longitudinal observational analytical study designed to evaluate the temporal relationship between serial fetal hemoglobin levels and the grade of retinopathy of prematurity. Infants were enrolled as a single cohort and subsequently categorized according to the presence and severity of ROP rather than being recruited using a case-control design.

Study Setting: The study was conducted in the ROP Clinic and Neonatal Intensive Care Unit (NICU) of S.C.B. Medical College and Hospital, Cuttack, Odisha, a tertiary referral centre providing neonatal and ophthalmic care. The PG Department of Ophthalmology, together with the associated NICU and Special Newborn Care Units, served as the primary recruitment sites.

Study Duration: The study was carried out over two years, from January 2024 to December 2025. This period allowed recruitment of eligible infants, serial HbF estimation, repeated ophthalmic examinations, follow-up, and completion of data collection.

Study Population and Sample Size

The study population consisted of preterm infants satisfying either of the following criteria:

- Birth weight ≤1500 g; or
- Birth weight ≤2000 g with one or more additional ROP-associated clinical risk factors, including sepsis, respiratory distress syndrome, hyperbilirubinemia requiring treatment, or blood transfusion.

A minimum sample size of 100 preterm infants was calculated using Fisher's z-transformation, assuming

an expected correlation coefficient of 0.30, 95% confidence level, and 80% power, with an allowance of 15% attrition due to mortality or loss to follow-up.

Inclusion Criteria

Preterm infants were included when they fulfilled the following criteria:

1. Birth weight ≤1500 g, or birth weight ≤2000 g with at least one predefined ROP risk factor.
2. Underwent ROP screening according to national guidelines.
3. Parental or guardian consent for serial blood sampling and ophthalmic examinations.

Exclusion Criteria: Infants were excluded if they were term infants (>37 weeks), had congenital ocular anomalies such as persistent fetal vasculature or congenital cataract, had severe congenital malformations or chromosomal disorders, died or were referred before completion of the first ROP examination, had incomplete HbF estimation at the required time points, or lacked parental consent.

Study Variables: The principal independent variable was serial HbF level (%), measured at birth and weekly from week 1 through week 6. Other independent variables included gestational age, birth weight, sepsis, respiratory distress syndrome, blood transfusion, hyperbilirubinemia, mechanical ventilation, duration of oxygen therapy, apnea, intraventricular hemorrhage, and necrotizing enterocolitis where present.

The dependent variable was ROP grade (Grade 0–4) according to the International Classification of Retinopathy of Prematurity (ICROP). Potential confounding variables included sex, nutritional status, surfactant therapy, postnatal weight gain, and oxygen saturation variability.

Baseline Assessment: Eligible neonates admitted to the NICU were screened daily. After informed consent, baseline data were recorded, including gestational age determined from the last menstrual period and/or New Ballard Score, birth weight, perinatal history, maternal risk factors, APGAR scores, and baseline hematological parameters including HbF.

Serial Fetal Hemoglobin Estimation: Blood samples of approximately 0.5–1 mL were collected at birth (day 1–2) and weekly thereafter for six weeks. HbF was quantified using high-performance liquid chromatography (HPLC). The thesis describes HPLC as the gold standard method used for HbF quantification.

ROP Screening and Grading: ROP examinations were performed by a trained ophthalmologist using indirect ophthalmoscopy with a +20 dioptre lens, pediatric eyelid speculum, and scleral depressor when required. Topical mydriatics were used according to neonatal safety protocols. The first examination was scheduled at **3**–4 weeks' postnatal age or 31 weeks postmenstrual age, whichever was later, followed by weekly or biweekly examinations according to the clinical findings. ROP was graded using the International Classification of Retinopathy of Prematurity (ICROP). Infants were followed until complete retinal vascularization, regression of ROP, or progression to disease requiring treatment.

Recorded Clinical and Ophthalmic Parameters: The study recorded weekly HbF percentage, total hemoglobin, oxygen saturation fluctuation profiles, ROP stage and zone, presence of plus disease, requirement for treatment with laser or anti-VEGF therapy, and relevant systemic neonatal complications. The same ophthalmologist performed the ROP examinations to reduce inter-observer variability.

Outcome Measures: The primary outcome was the correlation between fetal hemoglobin level and ROP grade.

Secondary outcomes included:

- The trend of HbF during the first six weeks of life.
- Association between HbF pattern and development or progression of ROP.
- Predictive ability of HbF for identifying infants at increased risk of severe ROP.

Statistical Analysis: Data were entered into Microsoft Excel, cross-verified, and analysed using JAMOVI version 2.6.44. Descriptive statistics were used for demographic and clinical characteristics. Pearson or Spearman correlation was planned to assess the relationship between HbF and ROP grade. Repeated-measures ANOVA or mixed-model analysis was used to evaluate weekly HbF trends, while multivariate logistic regression was planned to account for potential confounding factors such as gestational age, birth weight, and sepsis. ROC curve analysis was used to evaluate the potential predictive value of HbF for severe ROP. A p-value <0.05 was considered statistically significant.

Ethical Considerations and Quality Assurance: The study was approved by the Institutional Ethics Committee of S.C.B. Medical College and Hospital. Written informed consent was obtained from parents or guardians. Blood sampling was performed within neonatal safety limits, confidentiality was maintained, and infants requiring treatment for ROP received standard-of-care management without delay. Standard operating procedures were followed for sample collection and processing, all HbF measurements were performed in the same laboratory using the same HPLC system, and monthly data audits and multidisciplinary review meetings were conducted.

Results

Table 1: Gestational Age in weeks

Descriptives	
	Gestational_Age_wks
Mean	30.6
Std. error mean	0.247
95% CI mean lower bound	30.1
95% CI mean upper bound	31.1
Median	31
Standard deviation	2.47
Minimum	26
Maximum	34

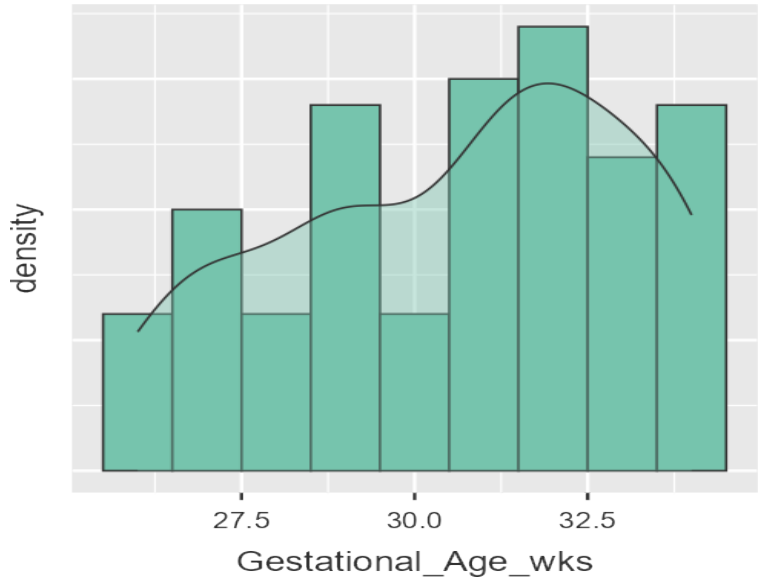

Figure 1: Gestational Age in weeks

Table 2: Birth weight

Descriptives	**Birth Weight (g)**
Mean	1300
Std. error mean	29.4
95% CI mean lower Bound	1241
95% CI mean upper Bound	1358
Median	1311
Standard deviation	294
Minimum	808
Maximum	1782

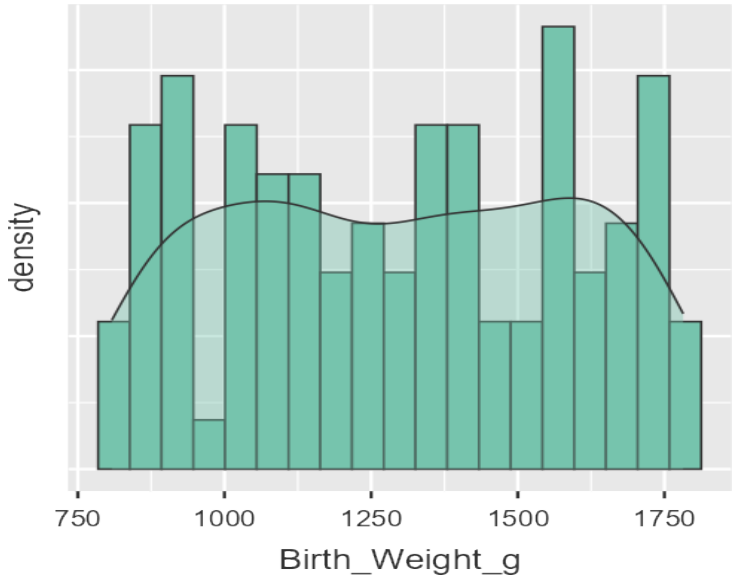

Figure 2: Birth weight

Table 3: Sepsis

Sepsis		
Sepsis	**Frequency**	**% of Total**
No	46	50.00%
Yes	54	50.00%

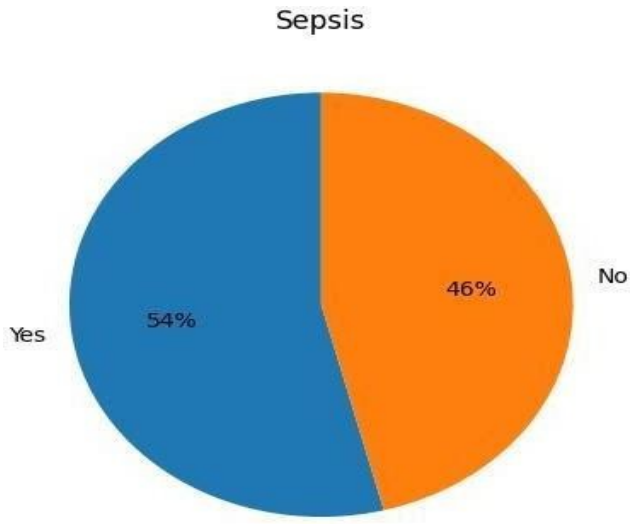

Figure 3: Sepsis

Table 4: RDS

RDS		
RDS	**Frequency**	**% of Total**
No	42	42.00%
Yes	58	58.00%

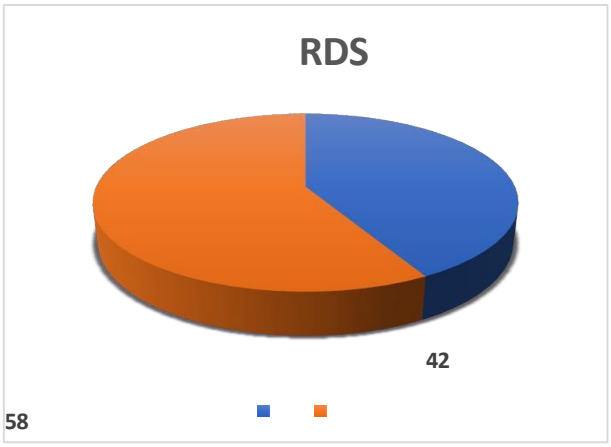

Figure 4: RDS

Table 5: Blood_Transfusion

Blood Transfusion		
Blood Transfusion	Frequency	% of Total
No	52	52.00%
Yes	48	48.00%

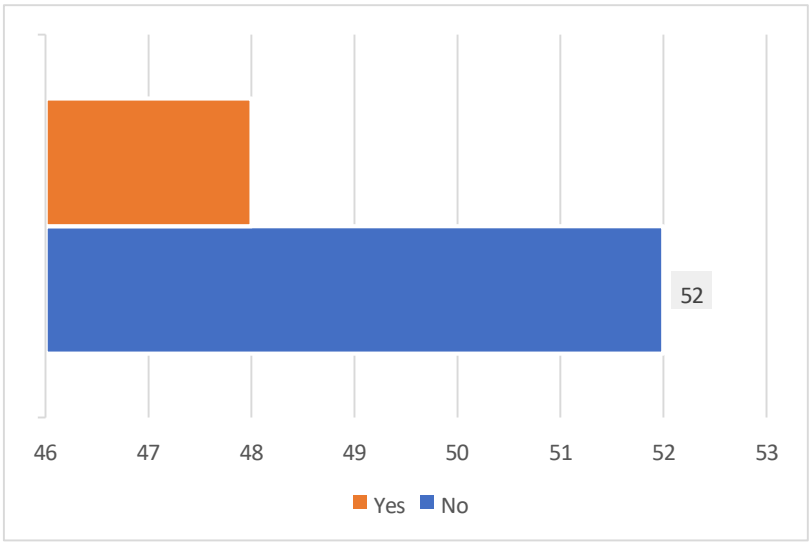

Figure 5: Blood_Transfusion

Table 6: Hyperbilirubinemia

Hyperbilirubinemia		
Hyperbilirubinemia	Frequency	% of Total
No	51	51.00%
Yes	49	49.00%

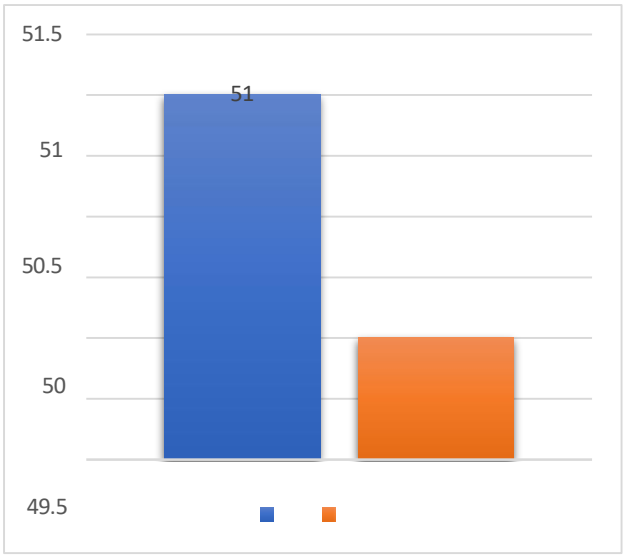

Figure 6: Hyperbilirubinemia

Table 7: Foetal Haemoglobin (HbF)

Descriptives							
	HbF_at_Birth	**HbF_Week1**	**HbF_Week2**	**HbF_Week3**	**HbF_Week4**	**HbF_Week5**	**HbF_Week6**
Mean	77.9	75.9	74	71.7	70	67.8	65.9
Std. error mean	0.687	0.684	0.69	0.692	0.731	0.76	0.757
95% CI mean lower bound	76.5	74.5	72.7	70.3	68.5	66.3	64.4
95% CI mean upper bound	79.2	77.2	75.4	73.1	71.4	69.3	67.4
Median	77.5	75.7	73.9	71.3	69.1	67.7	65.5
Standard deviation	6.87	6.84	6.9	6.92	7.31	7.6	7.57
Minimum	65.5	63.4	61.6	57.8	54.2	51.6	50.7
Maximum	89.5	87.8	86.6	85.7	84.6	83.1	82

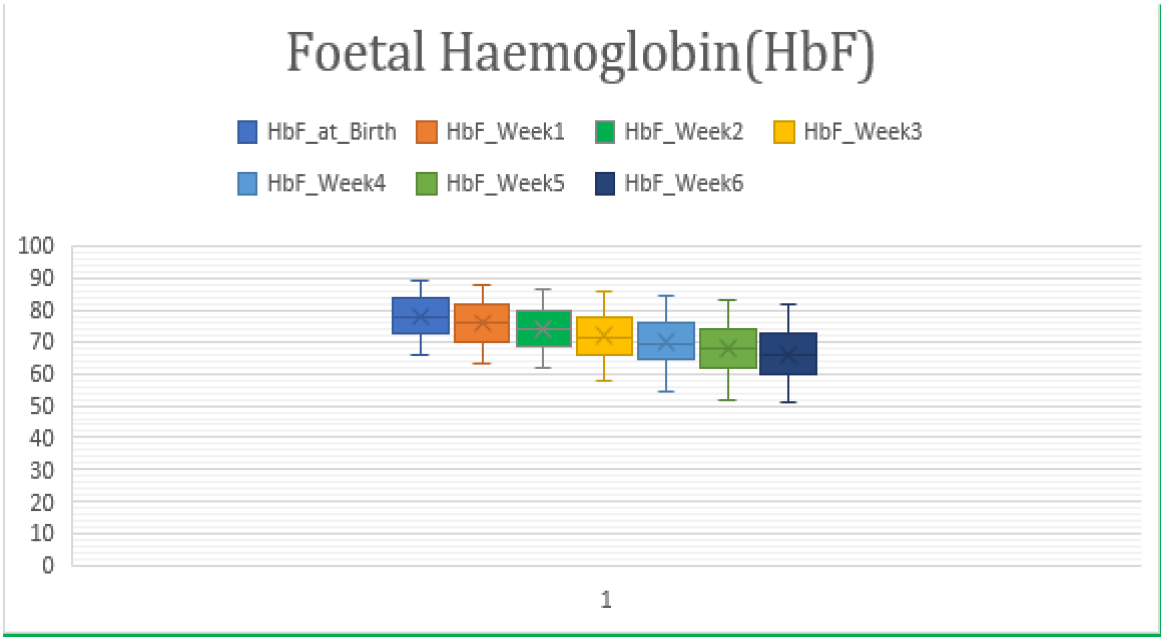

Figure 7: Foetal Haemoglobin (HbF)

Table 8: Paired T test between HbF parameters

Paired Samples T-Test					
			statistic	**df**	**p**
HbF_at_Birth	HbF_Week1	Student's t	36.58	99	<.001
	HbF_Week2	Student's t	35.74	99	<.001
	HbF_Week3	Student's t	33.78	99	<.001
	HbF_Week4	Student's t	34.89	99	<.001
	HbF_Week5	Student's t	37.11	99	<.001
	HbF_Week6	Student's t	34.67	99	<.001
HbF_Week1	HbF_Week2	Student's t	15.61	99	<.001
	HbF_Week3	Student's t	21.98	99	<.001
	HbF_Week4	Student's t	24.69	99	<.001
	HbF_Week5	Student's t	30.11	99	<.001
	HbF_Week6	Student's t	29.08	99	<.001
HbF_Week2	HbF_Week3	Student's t	10.69	99	<.001
	HbF_Week4	Student's t	16.71	99	<.001
	HbF_Week5	Student's t	22.24	99	<.001
	HbF_Week6	Student's t	22.41	99	<.001
HbF_Week3	HbF_Week4	Student's t	5.55	99	<.001
	HbF_Week5	Student's t	12.41	99	<.001
	HbF_Week6	Student's t	14.98	99	<.001
HbF_Week4	HbF_Week5	Student's t	6.1	99	<.001
	HbF_Week6	Student's t	9.85	99	<.001
HbF_Week5		Student's t	4.24	99	<.001
Note. H_a µMeasure 1 - Measure 2 ≠ 0					

Table 9: ANOVA Gestational age and Birth weight vs ROP

Group Descriptives						**One-Way ANOVA (Welch's)**			
	ROP_Grade	**N**	**Mean**	**SD**	**SE**	**F**	**df1**	**df2**	**p**
Gestational_Age_wks	0	21	33.4	0.676	0.148	99.42	4	35.3	<.001
	1	27	32.1	0.934	0.18				
	2	20	30	1.298	0.29				
	3	23	28.1	1.392	0.29				
	4	9	27.2	1.394	0.465				
Birth_Weight_g	0	21	1470.5	200.401	43.731	6.03	4	36.6	<.001
	1	27	1356.1	277.365	53.379				
	2	20	1304.7	288.181	64.439				
	3	23	1160.2	293.812	61.264				
	4	9	1075.4	287.682	95.894				

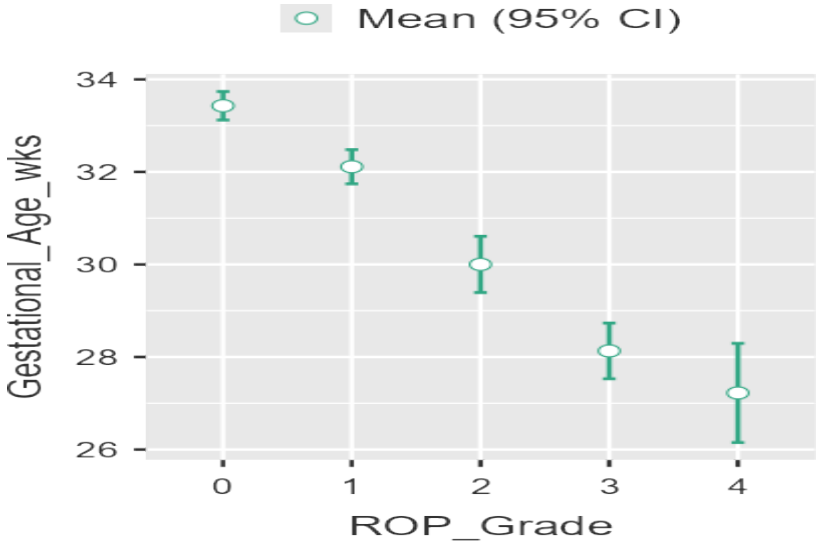

Figure 8: Gestational age vs ROP grade

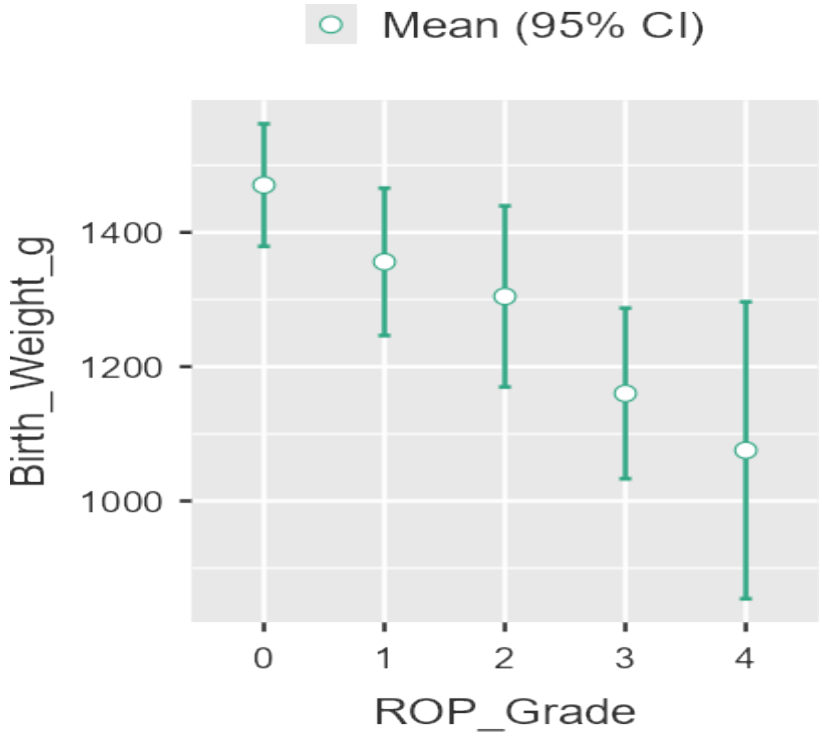

Figure 9: Birth weight vs ROP grade

Table 10: Multiple ANOVA HbF * ROP Grade

Estimated Marginal Means - HbF ✻ ROP_Grade					
		95% Confidence Interval			
ROP_Grade	HbF	Mean	SE	Lower	Upper
0	At Birth	76.2	1.52	73.2	79.2
	Week 1	74.2	1.51	71.2	77.2
	Week 2	72.6	1.53	69.5	75.6
	Week 3	69.8	1.52	66.8	72.8
	Week 4	68.6	1.62	65.4	71.8
	Week 5	66	1.68	62.7	69.3
	Week 6	64.4	1.67	61.1	67.7
1	At Birth	78	1.34	75.3	80.6
	Week 1	76	1.33	73.3	78.6
	Week 2	74.4	1.35	71.7	77
	Week 3	72	1.34	69.3	74.7
	Week 4	69.7	1.43	66.9	72.6
	Week 5	68.2	1.48	65.3	71.2
	Week 6	65.6	1.48	62.7	68.5
2	At Birth	78.9	1.55	75.8	81.9
	Week 1	76.8	1.55	73.7	79.9
	Week 2	74.6	1.56	71.5	77.7
	Week 3	72.4	1.56	69.3	75.5
	Week 4	71	1.66	67.7	74.3
	Week 5	68.5	1.72	65.1	71.9
	Week 6	67.1	1.71	63.7	70.5
3	At Birth	78.5	1.45	75.7	81.4
	Week 1	76.6	1.44	73.8	79.5
	Week 2	74.6	1.46	71.7	77.5
	Week 3	72.7	1.46	69.8	75.6
	Week 4	70.8	1.54	67.8	73.9
	Week 5	68.4	1.6	65.2	71.5
	Week 6	66.7	1.6	63.5	69.8
4	At Birth	77.6	2.31	73	82.2

	Week 1	75.5	2.31	70.9	80.1
	Week 2	73.8	2.33	69.2	78.4
	Week 3	71.2	2.33	66.6	75.9
	Week 4	69.6	2.47	64.7	74.5
	Week 5	67.4	2.57	62.4	72.5
	Week 6	66	2.56	60.9	71
Within Subjects Effects					
	Sum of Squares	**df**	**Mean Square**	**F**	**p**
HbF	9679.9	6	1613.31	376.978	<0.001
HbF ✻ ROP_Grade	28.3	24	1.18	0.276	1
Residual	2439.4	570	4.28		
Note. Type 3 Sums of Squares					
Between-Subjects Effects					
	Sum of Squares	**df**	**Mean Square**	**F**	**p**
ROP_Grade	590	4	148	0.433	0.785
Residual	32393	95	341		
Note. Type 3 Sums of Squares					

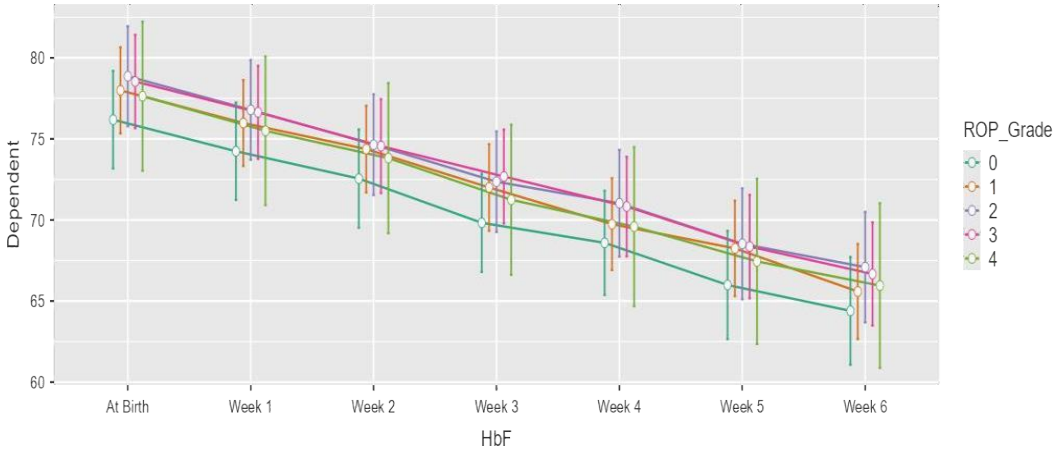

Figure 10: Multiple ANOVA HbF * ROP Grade

Discussion

Prematurity, oxygen exposure, systemic disease, nutritional condition, and haematological variables all affect retinal vascular development in retinopathy of prematurity (ROP), a complex ailment. In this prospective longitudinal study, 100 preterm infants' serial foetal haemoglobin (HbF) levels were assessed, and their correlation with ROP grade was investigated. The main conclusion was that, although the pattern of decline did not significantly vary across ROP grades, HbF decreased gradually and significantly from birth through the sixth postnatal week. Therefore, the current findings do not support HbF drop as an independent driver of ROP severity, despite the fact that HbF has a biologically reasonable involvement in retinal oxygenation. With a mean birth weight of 1300±294 g and a mean gestational age of 30.6±2.47 weeks, the study cohort was a therapeutically relevant group of premature newborns. The birth weight ranged from 808 to 1782 g, and the gestational age was between 26 and 34 weeks. Crucially, the results showed a definite negative correlation between ROP grade and maturity [4, 5].

Infants with grade 4 illness had a mean gestational age of 27.2 weeks, compared to 33.4 weeks for those without ROP. In a similar vein, the average birth weight decreased from roughly 1470 g in grade 0 to 1075 g in grade 4. Both correlations were significant ($p<0.001$). These results support the well-established significance of birth weight and gestational age as key factors influencing ROP. Lower gestational age and birth weight significantly raise the incidence of ROP, according to recent data. The current study's newborn risk-factor profile also demonstrated the cohort's clinical susceptibility. Of the neonates, 50% had sepsis, 58% had respiratory distress syndrome (RDS), 48% had blood transfusions, and 49% had hyperbilirubinemia. These results are significant because retinal vascular development may be impacted by systemic inflammation, respiratory instability, and transfusion-related alterations in oxygen delivery. Significant correlations between ROP and blood

transfusion, sepsis, low gestational age, lung illness, intraventricular haemorrhage, necrotising enterocolitis, and patent ductus arteriosus were found in a recent meta-analysis of extremely low birth weight infants. Similarly, gestational age and the length of oxygen treatment were found to be important factors in multivariable analysis in a prospective Indian research conducted in 2025 [6, 7].

The longitudinal HbF pattern was the most significant finding. At birth, the mean HbF was 77.9%; at weeks 1–6, it dropped to 75.9%, 74.0%, 71.7%, 70.0%, 67.8%, and 65.9%. There was a constant physiological shift from HbF to adult haemoglobin, as evidenced by all pairwise comparisons between subsequent HbF measurements being statistically significant ($p<0.001$). A significant impact of time on HbF was verified by the repeated-measures analysis ($F=376.978$, $p<0.001$). During postnatal maturation, this gradual reduction is biologically anticipated. The main discovery, however, was that the HbF trend was strikingly consistent throughout ROP grades. Both the between-subject effect of ROP grade ($F=0.433$, $p=0.785$) and the HbF × ROP-grade interaction ($F=0.276$, $p=1.000$) were not significant [8, 9].

Therefore, there was no statistically significant indication that infants with more severe ROP had a significantly different HbF trajectory, despite minor numerical changes in estimated marginal HbF values between classes. This result contrasts with the prospective Indian study by Prasad et al., which included 410 preterm infants and found that blood transfusion was substantially linked to ROP, while increased HbF was linked to decreased ROP prevalence and severity. Differences in sample size, population characteristics, HbF measurement timing and frequency, ROP categorisation, transfusion protocols, or adjustment for other neonatal variables could all contribute to the disparity. The longitudinal methodology of the current study is beneficial since it regularly assesses HbF instead of primarily depending on isolated data [10].

There is still a compelling biological case for researching HbF. While transfused adult red blood cells increase the amount of HbA and may change the delivery of oxygen to the retina, HbF has a higher affinity for oxygen than HbA. Hyperoxia and oxygen fluctuations are known elements of the pathophysiology of ROP. However, the present results indicate that HbF should not be viewed in a vacuum. Complex interplay between oxygenation, vascular maturity, inflammation, growth, and haematological variables lead to ROP. Therefore, rather than using HbF as a stand-alone biomarker, the study encourages further research into HbF as a component of multidimensional ROP prediction models. Although ROP prediction models can show strong discrimination, heterogeneity and insufficient confounding control continue to be significant drawbacks, according to a recent thorough study of these models. In the Indian setting, where timely ROP screening remains challenging, improved risk stratification could have substantial clinical value [11, 12].

Conclusion

The current prospective longitudinal investigation showed that among preterm newborns, foetal haemoglobin consistently and statistically significantly decreased from birth to the sixth postnatal week. However, the rate and amplitude of HbF loss were not substantially different between ROP grades, despite the biological plausibility of HbF regulating retinal oxygenation. Lower birth weight and gestational age, on the other hand, demonstrated significant correlations with worsening ROP, highlighting their ongoing significance as the main risk factors. The results imply that HbF by itself might not be sensitive or specific enough to forecast the severity of ROP. However, serial HbF evaluation is still biologically significant and could be used in future multifactorial prediction models that include postnatal development, transfusion, oxygen exposure, gestational age, birth weight, and sepsis. Larger multicentric longitudinal studies with detailed oxygenation and transfusion data are required to clarify whether specific HbF thresholds or trajectories have predictive value for severe ROP.

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