

A study of the factors associated with retinopathy of prematurity

QINGMIN MA^{1,2*}, XI LV^{2*}, JIANGYA WANG³, KEJUN LI², WENWEN TANG⁴, FANG FAN² and HAIFANG ZANG²

¹Department of Ophthalmology, People's Hospital of Bayingol Mongolian Autonomous Prefecture, Korla, Xinjiang Uygur Autonomous Region 841000, P.R. China; ²Department of Ophthalmology, Hebei General Hospital, Shijiazhuang, Hebei 050051, P.R. China; ³Department of Pediatrics, Hebei General Hospital, Shijiazhuang, Hebei 050051, P.R. China; ⁴Department of Ophthalmology, Shijiazhuang People's Hospital, Shijiazhuang, Hebei 050030, P.R. China

Received January 9, 2026; Accepted August 27, 2026

DOI: 10.3892/br.2026.2207

Abstract. The present study aimed to identify independent risk factors for retinopathy of prematurity (ROP) in preterm infants and to evaluate the predictive utility of maternal third-trimester apolipoprotein A1 (ApoA1) for early risk stratification. The present retrospective case-control study enrolled preterm infants who underwent ROP screening in the Departments of Neonatology and Ophthalmology in Hebei General Hospital (Shijiazhuang, China) between September 2018 and July 2023. Infants were stratified into a no-ROP group (n=22) or an ROP group (n=80) based on findings from dilated fundus examination. Maternal third-trimester lipid profiles and serial neonatal hematological and biochemical indices (collected within 24 h of birth and at 1 week of age) were extracted from electronic medical records. Binary logistic regression was performed to identify independent risk factors, and receiver operating characteristic (ROC) curves were constructed to evaluate predictive performance. Univariate analysis revealed statistically significant differences between the no-ROP and ROP groups with regard to gestational age, birth weight, 1-min Apgar score, neonatal pneumonia, neonatal bronchopulmonary dysplasia, neonatal respiratory distress syndrome, sepsis, blood transfusion, maternal apolipoprotein A1 (ApoA1), platelet count at 24 h and 1 week, 1-week mean platelet volume, 1-week hemoglobin, 1-week neutrophil-to-lymphocyte ratio and 1-week lymphocyte-to-monocyte ratio (all $P<0.05$). Multivariate logistic regression analysis identified reduced maternal third-trimester ApoA1 as the sole independent risk factor for ROP ($P<0.05$). ROC analysis demonstrated that maternal ApoA1 <0.584 g/l predicted increased ROP risk

with 90.9% sensitivity and 67.5% specificity (area under the curve, 0.768; 95% confidence interval, 0.661-0.875; $P<0.001$). In conclusion, reduced maternal third-trimester ApoA1 is an independent predictor of ROP development, demonstrating high sensitivity for early risk identification. These findings support the integration of maternal lipid profiling into ROP screening algorithms and underscore the clinical importance of enhanced surveillance for infants born to mothers with reduced ApoA1 levels.

Introduction

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disorder affecting premature infants and representing the leading cause of preventable childhood blindness globally. In recent decades, advances in neonatal intensive care have substantially improved the survival rates of premature infants, particularly those with low birth weight (BW) and low gestational age (GA), while simultaneously increasing the prevalence of ROP. A total of ~50,000 new cases of ROP are diagnosed annually worldwide, resulting in irreversible blindness in a notable proportion of affected individuals. China accounts for ~4,000 cases, representing 1.9% of childhood blindness in children <5 years of age (1) ROP presents a substantial clinical challenge for both neonatologists and ophthalmologists. The pathogenesis of ROP is characterized by two phases: Initial vaso-obliteration driven by hyperoxia-induced suppression of angiogenic factors, followed by hypoxia-driven pathological neovascularization. Low GA and low BW remain the strongest established risk factors, although the contribution of postnatal hematological, inflammatory and maternal metabolic factors warrants further investigation (2).

Accordingly, it is essential to systematically investigate the risk factors associated with ROP and implement timely and evidence-based interventions to prevent disease progression. The present study aimed to investigate the association between clinical characteristics, blood count indices, biochemical parameters and other clinical indicators in preterm infants and ROP development, with the objective of establishing a scientific foundation for ROP prevention, treatment optimization and improved long-term outcomes. In our previous analysis restricted to the ROP-only subset of the same cohort, GA ≤ 30.5 weeks was identified as the strongest predictor of severe ROP (3); however, that study could not address whether

Correspondence to: Professor Qingmin Ma, People's Hospital of Bayingol Mongolian Autonomous Prefecture, 150 Middle Section of Fuxing Avenue, Yingxia, Korla, Xinjiang Uygur Autonomous Region 841000, P.R. China
E-mail: 90030202@hebmu.edu.cn

*Contributed equally

Key words: retinopathy of prematurity, risk factors, apolipoprotein A1, birth weight, lipid profile

maternal metabolic factors predict ROP occurrence before disease onset. The present study was designed to fill this gap by including the complete screened cohort with a no-ROP control group.

Materials and methods

Study design and population. The present retrospective case-control study was conducted at Hebei General Hospital (Shijiazhuang, China), analyzing clinical data from preterm infants admitted to the Departments of Neonatology and Ophthalmology between September 2018 and July 2023. Medical records were retrospectively accessed and data were extracted between August 2024 and March 2025. Statistical analysis was performed between April 2025 and June 2025.

All enrolled infants underwent comprehensive fundus examination for ROP screening according to established protocols.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hebei General Hospital [approval no. 115 (2024)]. Due to the retrospective nature of the present study utilizing existing medical records, the Ethics Committee waived the requirement for informed consent. Appropriate measures were implemented to ensure patient confidentiality and compliance with data protection standards.

Participants

Inclusion criteria. The ROP group consisted of preterm infants with a BW <3,000 g, a GA <37 weeks and a confirmed diagnosis of ROP based on fundus screening examination. The control group (no-ROP) consisted of preterm infants with a GA <37 weeks and a BW <3,000 g admitted to the hospital during the same study period who demonstrated no evidence of ROP on initial screening and had no retinal lesions on long-term follow-up. Follow-up continued until retinal vascularization reached zone III in both eyes without any pre-threshold or threshold lesions.

Exclusion criteria. Infants were excluded if they met any of the following criteria: i) GA $\geq$ 37 weeks or BW $\geq$ 3,000 g at birth; ii) incomplete or unavailable clinical data; iii) inability to complete follow-up to zone III retinal vascularization in both eyes without pre-threshold or threshold lesions, or if visual pathway integrity could not be confirmed through clinical evaluation and imaging examination (ultrasound or magnetic resonance imaging if necessary); iv) presence of systemic conditions affecting hematological and biochemical parameters, including blood disorders, genetic metabolic diseases or other systemic diseases; and v) other organic ocular diseases or systemic diseases known to cause ocular manifestations.

ROP diagnosis and classification. ROP diagnosis and classification were based on the International Classification of Retinopathy of Prematurity Third Edition (4). Specifically, classification is based on i) zone, the location of disease; ii) stage, the appearance of disease at the avascular-vascular junction; and iii) circumferential extent of disease (measured in clock hours). Additional key components include the presence of preplus or plus disease and the presence of aggressive ROP. Infants were stratified

into either the no-ROP group or ROP group according to dilated fundus examination findings.

Fundus examination. All fundus examinations were performed by two independent ophthalmologists in a masked fashion to minimize subjective bias, utilizing RetCam 3 digital imaging system (Clarity Medical Systems). Initial screening was performed at 4–6 weeks postnatal age or 31–32 weeks postmenstrual age. Subsequent screening intervals were determined based on initial findings and progression of retinal vascularization, with continued follow-up or treatment implementation until retinal vascularization reached zone III or 45 weeks postmenstrual age was achieved, provided no threshold or pre-threshold lesions were present. Pupils were dilated using topical tropicamide ophthalmic drops (0.5%) instilled bilaterally at 5–10 min intervals, with repeated instillation at least 4 times until maximum mydriasis was achieved. Topical anesthesia was provided with 0.5% proparacaine hydrochloride. Following appropriate infant restraint and head stabilization, sterile pediatric eyelid specula were used to maintain adequate eyelid separation. Gatifloxacin ophthalmic gel was applied to the eyelid margins prior to comprehensive digital fundus imaging using the RetCam 3 system.

Of 150 eligible infants screened, 124 (82.7%) completed follow-up until retinal vascularization reached zone III or 45 weeks postmenstrual age without threshold or pre-threshold lesions. A total of 22 infants were excluded due to inadequate documentation, resulting in 102 infants for final analysis.

Data collection. Comprehensive clinical data were systematically collected for all included preterm infants, including demographic information (sex), GA, BW, mode of delivery, ROP screening results, maternal history of gestational diabetes mellitus (GDM) or gestational hypertension, 1-min Apgar score, and neonatal complications such as pneumonia, neonatal bronchopulmonary dysplasia (NBPD), neonatal respiratory distress syndrome (NRDS), neonatal sepsis and requirement for blood transfusion. Neonatal blood parameters were obtained from complete blood count and biochemical analyses performed within 24 h of birth and at 1 week of age, including white blood cell count (WBC), neutrophil count (N), monocyte count (M), lymphocyte count (L), platelet count (PLT), mean platelet volume (MPV), hemoglobin (Hb), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), apolipoprotein B (ApoB), high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1). Derived indices were calculated from these parameters, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII). Additionally, maternal lipid profiles, including TC, TG, LDL, ApoB, HDL and ApoA1, were collected from the third trimester of pregnancy. Laboratory measurements were performed using standardized automated hematological analyzers and biochemical methods according to hospital clinical laboratory standards. Units for measurement were as follows: $10^9/l$ for WBC, N, M, L and PLT; g/l for Hb; and fl for MPV. Maternal blood samples were collected during late pregnancy, specifically between 36 and 40 weeks of gestation (mean collection time, 38 weeks of gestation).

Statistical analysis. Statistical analysis was performed using SPSS version 24.0 (IBM Corp.). Normally distributed continuous variables are expressed as mean $\pm$ standard deviation (SD) and compared between groups using the independent samples Student's t-test. Non-normally distributed measurement data are expressed as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables are expressed as number (percentage) and were compared between groups using the χ^2 test or Fisher's exact probability test, as appropriate. To identify independent risk factors for ROP, a multivariate binary logistic regression model was constructed using variables that demonstrated statistical significance on univariate analysis ($P \leq 0.05$) as independent variables, with ROP occurrence as the dependent variable. The following 16 variables were included in the multivariate model: GA, BW, maternal third-trimester ApoA1, 1-min Apgar score, neonatal pneumonia, NBPD, neonatal sepsis, NRDS, blood transfusion requirement, 24-h PLT, 1-week PLT, 1-week MPV, 1-week Hb, 1-week NLR, 1-week LMR and 1-week ApoA1. Variables with univariate P-values ≤ 0.05 were retained in the logistic regression model (significance level $\alpha = 0.05$). Receiver operating characteristic (ROC) curves were plotted for independent risk factors, and the area under the curve (AUC) was calculated to evaluate early predictive value. The optimal diagnostic threshold was determined by maximizing the Youden index, with corresponding sensitivity and specificity calculated. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Study population characteristics. A total of 102 preterm infants who underwent ROP screening at Hebei General Hospital between September 2018 and July 2023 were included in this study. The cohort comprised 22 infants in the no-ROP group and 80 infants in the ROP group.

Demographic and clinical characteristics. Comparison of general clinical data between the ROP and no-ROP groups revealed no significant differences with regard to sex distribution ($\chi^2 = 0.268$; $P = 0.605$), mode of delivery ($\chi^2 = 2.374$; $P = 0.123$), maternal GDM ($\chi^2 = 0.358$; $P = 0.549$), maternal gestational hypertension ($\chi^2 = 0.202$; $P = 0.653$) or maternal third-trimester lipid parameters, including TC ($Z = -1.524$; $P = 0.128$), TG ($Z = -0.053$; $P = 0.958$), LDL ($Z = -1.344$; $P = 0.179$), apolipoprotein B ($Z = -0.819$; $P = 0.413$) and HDL ($Z = -1.218$; $P = 0.223$). Conversely, statistically significant differences were identified between groups with regard to GA ($Z = -6.328$; $P < 0.001$), BW ($Z = -6.062$; $P < 0.001$), maternal third-trimester ApoA1 ($Z = -3.846$; $P < 0.001$), 1-min Apgar score ($Z = -2.103$; $P = 0.035$), neonatal pneumonia ($\chi^2 = 6.841$; $P = 0.006$), NBPD ($\chi^2 = 20.443$; $P < 0.001$), neonatal sepsis ($\chi^2 = 6.421$; $P = 0.011$), NRDS ($\chi^2 = 12.577$; $P < 0.001$) and requirement for blood transfusion ($\chi^2 = 28.728$; $P < 0.001$) (Table I).

Blood parameters within 24 h of birth. Comparative analysis of hematological parameters in preterm infants from the ROP and no-ROP groups obtained within 24 h of birth revealed the following findings: PLT at 24 h after birth showed a statistically significant difference between groups ($t = 3.157$; $P = 0.002$).

By contrast, WBC ($Z = -1.639$; $P = 0.101$), N ($Z = -1.843$; $P = 0.065$), MPV ($Z = -1.902$; $P = 0.057$), Hb ($t = 0.241$; $P = 0.810$), NLR ($Z = -1.318$; $P = 0.187$), LMR ($Z = -0.350$; $P = 0.726$), PLR ($Z = -1.220$; $P = 0.222$) and SII ($Z = -2.864$; $P = 0.061$) showed no significant intergroup differences. Detailed results are presented in Table II.

Blood parameters at 1 week after birth. Comparative analysis of hematological parameters in preterm infants from the ROP and no-ROP groups obtained at 1 week postnatal age showed the following: At 1 week after birth, significant differences were identified with regard to PLT ($Z = -2.815$; $P = 0.005$), MPV ($t = -5.006$; $P < 0.001$), Hb ($t = 3.710$; $P < 0.001$), NLR ($Z = -2.343$; $P = 0.019$), LMR ($Z = -4.271$; $P < 0.001$) and ApoA1 ($Z = 3.025$; $P = 0.002$) between the two groups. No significant differences were observed with regard to WBC ($Z = 0.696$; $P = 0.487$), N ($Z = -1.216$; $P = 0.224$), PLR ($Z = -1.725$; $P = 0.085$), SII ($Z = -0.220$; $P = 0.826$), TC ($Z = -0.667$; $P = 0.505$), TG ($Z = -1.127$; $P = 0.260$), LDL ($Z = -0.891$; $P = 0.373$), ApoB ($Z = -1.592$; $P = 0.111$) or HDL ($Z = -1.245$; $P = 0.213$) between groups (Table III).

Multivariate logistic regression analysis of ROP risk factors. Multivariate binary logistic regression analysis was performed to identify independent risk factors for ROP development. Variables demonstrating significance on univariate analysis ($P < 0.05$) were entered as independent variables, with ROP occurrence as the dependent variable. The following 16 variables were analyzed: GA, BW, maternal third-trimester ApoA1, 1-min Apgar score, neonatal pneumonia, NBPD, neonatal sepsis, NRDS, blood transfusion requirement, 24-h PLT, 1-week PLT, 1-week MPV, 1-week Hb, 1-week NLR, 1-week LMR and 1-week ApoA1. Results demonstrated that reduced maternal third-trimester ApoA1 was a significant risk factor for ROP ($P = 0.027$). Due to the total sample size of 102 cases with unequal group distribution (80 ROP cases vs. 22 no-ROP cases), there exists a potential for model overfitting, particularly in retrospective designs where imbalanced groups may compromise prediction accuracy for rare events. However, this imbalance reflects the clinical reality of the high ROP incidence rate observed in this cohort (78.4%), and model robustness was enhanced through incorporation of multiple clinically relevant variables, including established strong risk factors such as low GA and low BW. Multivariate analysis results confirmed that reduced maternal third-trimester ApoA1 remained an independent risk factor for ROP ($P = 0.027$) after controlling for other significant covariates, including GA, BW and NBPD (Table IV).

Predictive value of independent risk factors for early ROP identification. To assess the early predictive performance of maternal third-trimester ApoA1 for ROP development, ROC curve analysis was performed. The area under the ROC curve for maternal ApoA1 was 0.768 (95% CI, 0.661-0.875; $P < 0.001$), indicating moderate discriminatory ability. The optimal cutoff value determined by maximizing the Youden index was 0.584 g/l, corresponding to a sensitivity of 90.9% and a specificity of 67.5% (Table V; Fig. 1). The Youden index, as a balanced measure integrating both sensitivity and specificity, ensures optimized clinical threshold selection and supports the practical application of ApoA1 in clinical

Table I. Comparison of general data between preterm infants in the no-ROP (n=22) and ROP (n=80) groups.

Parameter	No-ROP group	ROP group	Statistical value	P-value
Sex, n (%)			$\chi^2=0.268$	0.605
Male	14 (63.64)	46 (57.50)		
Female	8 (36.36)	34 (42.50)		
GA, weeks	36.00 (0.00)	30.73 (3.72)	Z=-6.328	<0.001
BW, g	2,459.32 (631.62)	1,295.00 (656.00)	Z=-6.062	<0.001
Mode of delivery, n (%)			$\chi^2=2.374$	0.123
Cesarean section	19 (86.36)	56 (70.00)		
Natural birth	3 (13.64)	24 (30.00)		
Gestational diabetes, n (%)	6 (27.27)	17 (21.25)	$\chi^2=0.358$	0.549
Gestational hypertension, n (%)	5 (22.73)	22 (27.50)	$\chi^2=0.202$	0.653
Lipid parameters in the third trimester of pregnancy				
TC, mmol/l	6.42 (0.53)	6.15 (1.06)	Z=-1.524	0.128
TG, mmol/l	2.99 (1.19)	3.13 (0.98)	Z=-0.053	0.958
LDL, mmol/l	3.67 (0.36)	3.50 (0.67)	Z=-1.344	0.179
ApoB, g/l	1.13 (0.24)	1.07 (0.24)	Z=-0.819	0.413
HDL, mmol/l	1.77 (0.08)	1.65 (0.36)	Z=-1.218	0.223
ApoA1, g/l	2.15 (0.18)	1.91 (0.35)	Z=-3.846	<0.001
1-min Apgar score	10.00 (0.00)	10.00 (2.00)	Z=-2.103	0.035
Neonatal pneumonia, n (%)	0 (0.00)	20 (25.00)	$\chi^2=6.841$	0.006
NBPD, n (%)	0 (0.00)	43 (53.75)	$\chi^2=20.443$	<0.001
Neonatal sepsis, n (%)	0 (0.00)	19 (23.75)	$\chi^2=6.421$	0.011
NRDS, n (%)	2 (9.09)	41 (51.25)	$\chi^2=12.577$	<0.001
Blood transfusion, n (%)	1 (4.56)	55 (68.75)	$\chi^2=28.728$	<0.001

Data are presented as mean $\pm$ standard deviation or median (interquartile range), unless otherwise specified. ROP, retinopathy of prematurity; GA, gestational age; BW, birth weight; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; ApoB, Apolipoprotein B; HDL, high density lipoprotein; ApoA1, Apolipoprotein A1; NBPD, neonatal bronchopulmonary dysplasia; NRDS, neonatal respiratory distress syndrome.

risk stratification. Although univariate analysis demonstrated significant correlations between neonatal parameters such as BW (Z=-6.062; P<0.001) and ROP, multivariate logistic regression confirmed that maternal third-trimester ApoA1 remained an independent predictor after adjustment for these factors. The superior AUC of 0.768 for ApoA1 compared with traditional neonatal risk factors highlights its complementary value as a maternal biomarker, particularly for early risk stratification of high-risk preterm infants with reduced ApoA1 levels. The high sensitivity of 90.9% results in a relatively low false-negative rate, indicating that ApoA1 screening can effectively minimize the risk of missed diagnoses in premature infants at high risk for ROP. Conversely, the moderate specificity of 67.5% results in a moderate false-positive rate that may necessitate additional surveillance, though the high sensitivity overall enhances the clinical utility of early identification. These findings support the incorporation of maternal third-trimester ApoA1 assessment into ROP screening algorithms, with particular emphasis on intensified monitoring of neonates born to mothers with ApoA1 levels <0.584 g/l. The ROC analysis of maternal ApoA1 (Fig. 1) demonstrates its predictive utility for ROP, particularly regarding high sensitivity and superior

discriminatory performance compared with conventional approaches relying exclusively on neonatal indicators. This evidence provides a foundation for clinical implementation and suggests prioritizing ApoA1 evaluation during routine third-trimester maternal lipid screening to facilitate timely intervention in ROP prevention. However, due to limitations inherent to the single-center retrospective design and sample size (n=102), future multicenter prospective validation studies will be needed to confirm the generalizability and clinical applicability of these findings.

Discussion

Low GA and low BW represent the two most strongly established risk factors for ROP development. Preterm infants are born with structurally immature retinal vasculature and underdeveloped organ systems, rendering them susceptible to diverse internal and external environmental stressors that accelerate ROP pathogenesis. As GA decreases and BW declines, preterm infants face increased exposure to established ROP risk factors, including hyperoxic therapy and infectious complications, with correspondingly worse developmental status predisposing to rapid

Table II. Comparison of blood parameters of preterm infants within 24 h of birth between the ROP (n=80) and no-ROP (n=22) groups.

Blood parameters	No-ROP group	ROP group	Statistical value	P-value
WBC, 10 ⁹ /l	10.52 (5.29)	9.25 (5.74)	Z=-1.639	0.101
N, 10 ⁹ /l	4.51 (2.97)	3.34 (5.37)	Z=-1.843	0.065
PLT, 10 ⁹ /l	287.09±62.11	234.38±71.16	t=3.157	<0.01
MPV, 10 ⁹ /l	9.92 (0.92)	10.20 (1.10)	Z=-1.902	0.057
Hb, g/l	168.27±14.49	167.11±21.20	t=0.241	0.810
NLR	0.98 (0.61)	0.83 (1.60)	Z=-1.318	0.187
LMR	7.28 (2.89)	7.28 (5.75)	Z=-0.350	0.726
PLR	65.22 (18.23)	53.41 (40.91)	Z=-1.220	0.222
SII	202.15 (159.44)	186.52 (324.37)	Z=-2.864	0.061

Data are presented as mean ± standard deviation or median (interquartile range), unless otherwise specified. ROP, retinopathy of prematurity; WBC, white blood cell count; N, neutrophil count; PLT, platelet count; MPV, mean platelet volume; Hb, hemoglobin; NLR, the ratio of neutrophils to lymphocytes; LMR, the ratio of lymphocytes to monocytes; PLR, the ratio of platelet count to lymphocytes; SII, systemic immune-inflammation index.

Table III. Comparison of blood parameters 1 week after birth between preterm infants in the no-ROP (n=22) and ROP groups (n=80).

1-Week blood parameters	No-ROP group	ROP group	Statistical value	P-value
WBC, 10 ⁹ /l	9.67 (2.82)	10.04 (6.96)	Z=0.696	0.487
N, 10 ⁹ /l	4.31 (2.14)	4.71 (4.80)	Z=-1.216	0.224
PLT, 10 ⁹ /l	289.67 (125.55)	209.00 (127.00)	Z=-2.815	^b
MPV, 10 ⁹ /l	10.60±0.93	11.65±0.86	t=-5.006	^c
Hb, g/l	154.00±18.04	137.17±19.05	t=3.710	^c
NLR	1.64 (0.77)	1.34 (1.18)	Z=-2.343	^a
LMR	4.32 (1.61)	2.82 (1.76)	Z=-4.271	^c
PLR	75.52 (31.54)	63.84 (34.11)	Z=-1.725	0.085
SII	325.22 (207.81)	305.57 (330.14)	Z=-0.220	0.826
TC, mmol/l	3.07 (0.73)	2.99 (1.14)	Z=-0.667	0.505
TG, mmol/l	0.81 (0.36)	0.69 (0.71)	Z=-1.127	0.260
LDL, mmol/l	2.10 (0.63)	1.91 (0.80)	Z=-0.891	0.373
ApoB, g/l	0.51 (0.16)	0.45 (0.15)	Z=-1.592	0.111
HDL, mmol/l	0.92 (0.27)	0.88 (0.39)	Z=-1.245	0.213
ApoA1, g/l	0.96 (0.07)	0.81 (0.29)	Z=3.025	^b

Data are presented as mean ± standard deviation or median (interquartile range), unless otherwise specified. ^aP<0.05, ^bP<0.01 and ^cP<0.001. ROP, retinopathy of prematurity; WBC, white blood cell count; N, neutrophil count; PLT, platelet count; MPV, mean platelet volume; Hb, hemoglobin; NLR, the ratio of neutrophils to lymphocytes; LMR, the ratio of lymphocytes to monocytes; PLR, the ratio of platelet count to lymphocytes; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; ApoB, Apolipoprotein B; HDL, high density lipoprotein; ApoA1, Apolipoprotein A1.

disease progression and severe manifestations. Hu *et al* (5) demonstrated that increased GA and higher BW conferred protective effects against ROP development. Consistent with these findings, in the present cohort, preterm infants in the ROP group demonstrated significantly lower GA and BW compared with the no-ROP group, confirming that diminished GA and BW represent independent risk factors for ROP pathogenesis.

Kim *et al* (6) conducted a retrospective summary of the literature examining the association between delivery mode and ROP development and found the relationship to be controversial. Some investigations identified increased ROP risk with vaginal delivery, others with cesarean delivery and several identified no association with delivery mode. In the present study, no significant association was identified between delivery method and ROP severity, which may be attributable

Table IV. Results of multi-factor logistic regression analysis affecting retinopathy of prematurity occurrence.

Risk factor	Regression coefficient	Standard error	Wald	Df	P-value	OR (95% CI)
ApoA1 in late pregnancy	-7.219	3.269	4.875	1	0.027	0.001 (0.000-0.444)

ApoA1, apolipoprotein A1; OR, odds ratio; CI, confidence interval; Df, degrees of freedom.

Table V. Early predictive value of maternal ApoA1 for retinopathy of prematurity occurrence.

Indicators	AUC	Sensitivity	Specificity	Optimal threshold	95% CI	P-value
ApoA1 in late pregnancy	0.768	0.909	0.675	0.584	0.661-0.875	<0.001

AUC, area under the curve; CI, confidence interval; ApoA1, apolipoprotein A1.

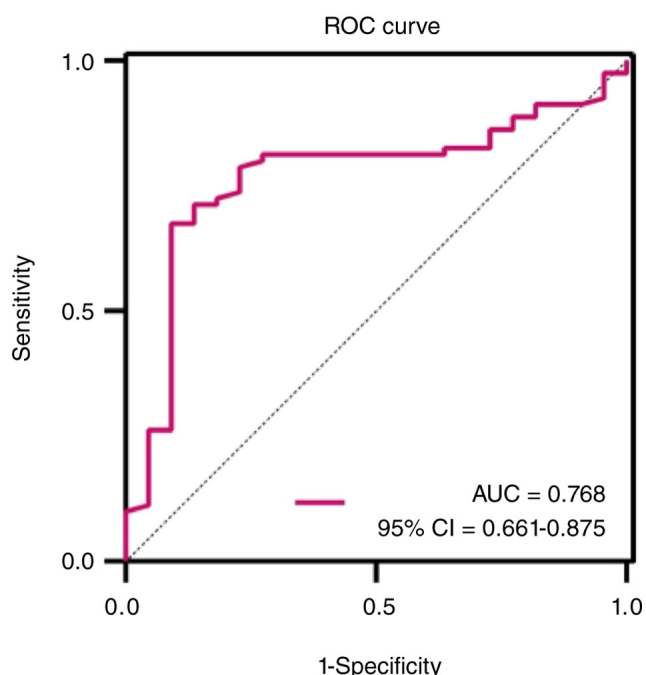


Figure 1. ROC curve of maternal third-trimester ApoA1 for the early prediction of ROP. The AUC is 0.768 (95% CI, 0.661-0.875; $P < 0.001$). The optimal cut-off value of 0.584 g/l (Youden index maximum) yields a sensitivity of 90.9% and a specificity of 67.5% for identifying infants at increased ROP risk associated with reduced maternal ApoA1 levels. ROC, receiver operating characteristic; ROP, retinopathy of prematurity; ApoA1, apolipoprotein A1; AUC, area under the curve.

to incomplete adjustment for potentially confounding factors such as peripartum antimicrobial administration and intra-uterine infection risk.

According to the American College of Obstetricians and Gynecologists (7), gestational hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg measured on at least 2 separate occasions or at intervals > 4 h after 20 weeks of gestation, with preeclampsia characterized by hypertension accompanied by proteinuria or other end-organ manifestations. Contemporary investigations have highlighted the importance of soluble fms-like

tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), with the sFlt-1/PlGF ratio demonstrating substantial value for preeclampsia diagnosis and prognosis (8). In preeclamptic pregnancies, sFlt-1 concentrations are elevated while PlGF levels are reduced compared with those in normotensive pregnancies, with the sFlt-1/PlGF ratio providing greater diagnostic utility than measurement of either biomarker alone (9,10). The maternal antiangiogenic state characteristic of gestational hypertension and preeclampsia may paradoxically provide neonatal protection against ROP development.

Yu *et al* (11), in a retrospective cohort investigation, demonstrated that preeclampsia was associated with reduced ROP risk, identifying it as a protective factor. Conversely, gestational hypertension showed no notable association with ROP. A meta-analysis by Chan *et al* (12) demonstrated no significant association between hypertensive disorders of pregnancy and ROP, consistent with the findings of Yu *et al* (11). In the present analysis, gestational hypertension similarly demonstrated no significant association with ROP development. Limited literature, both domestically and internationally, has evaluated GDM in relation to ROP pathogenesis. As both ROP and diabetic retinopathy represent retinal vascular diseases with pathological leakage and neovascularization of damaged retinal vessels, glucose metabolism may influence ROP development. Through retrospective analysis, Opara *et al* (13) identified an association between GDM and ROP with increasing severity correlation. The study investigated perinatal factors influencing ROP severity and identified GDM association only with stage 3 ROP. The present study identified no significant association between GDM and ROP development or progression, which we hypothesize may relate to methodological differences, particularly the inclusion of infants with BW $< 3,000$ g (compared with $< 1,500$ g in prior studies). Given that smaller infants demonstrate higher ROP severity risk and the relatively modest sample size in this investigation, this difference may explain the absence of statistical significance (13). The mechanistic associations between prenatal factors and ROP remain incompletely understood, necessitating additional high-quality prospective cohort investigations.

The Apgar score provides rapid assessment of neonatal condition based on respiratory effort, heart rate, skin color,

muscle tone and reflex irritability, with a maximum score of 10. This scoring system is simple, expeditious, inexpensive, and applicable to both preterm and term infants, serving an important role in identifying neonatal asphyxia. Clinically, a neonatal asphyxia diagnosis relies on Apgar scoring and recognition that asphyxia fundamentally involves hypoxemia, hypercapnia and metabolic acidosis secondary to impaired perinatal gas exchange. Ali *et al* (14) demonstrated that both 1-min and 5-min Apgar scores were significantly and inversely associated with ROP severity. Marinov *et al* (15) identified low 5-min Apgar score (≤ 6) as a risk factor for ROP progression requiring treatment, with increasingly lower scores predicting more severe ROP manifestations and worse general clinical status. The present investigation identified that 1-min Apgar scores were significantly higher in preterm infants without ROP compared with those in the ROP group, with infants with mild ROP demonstrating significantly higher 1-min Apgar scores than those with severe ROP.

NBPD and NRDS represent prevalent causes of early neonatal respiratory distress. NRDS results from pulmonary immaturity with insufficient pulmonary surfactant production, whereas NBPD develops as a consequence of aberrant lung injury repair following hyperoxic hyperventilation therapy. Both represent leading causes of early neonatal respiratory failure. Oxygen therapy is essential for managing NBPD and NRDS to prevent respiratory decompensation in lungs compromised by developmental immaturity. The antioxidant defense system remains immature in preterm infants, rendering them vulnerable to hyperoxia-induced oxidative injury through excessive free radical generation, dysregulation of pro-oxidant pathways and resulting tissue damage that promotes ROP pathogenesis. Additionally, hyperoxia impairs lung development through inhibition of alveolar formation and angiogenesis, compounding oxygen injury risk in the absence of adequate pulmonary surfactant. Furthermore, growth factors implicated in NBPD pathogenesis may similarly influence retinal vascular development, including alterations in VEGF, insulin-like growth factor-1 (IGF-1) and transforming growth factor- β secretion, that characterize both conditions (3,16). Podraza *et al* (16), investigating ROP and NBPD severity association, stratified neonates into NBPD-positive and NBPD-negative groups and demonstrated that NBPD-positive neonates exhibited substantially greater odds of advanced ROP development, with oxygen therapy emerging as a critical pathogenic factor for both disorders. Lin *et al* (17), in a cohort investigation, identified that respiratory distress syndrome (RDS) carried a 2.5-fold increased ROP incidence relative to non-RDS neonates. Consistent with these observations, the present study demonstrated increased NBPD and NRDS incidence in the ROP group compared with that in the no-ROP group, with higher incidence in severe ROP compared with mild ROP, and all differences achieving statistical significance.

Infection provokes inflammatory cascade activation with enhanced production of pro-inflammatory mediators, including interleukin (IL)-6, IL-8, tumor necrosis factor- α (TNF- α) and thromboxane A₂, which damage vascular endothelium, induce retinal hypoxia and stimulate VEGF release. Both maternal systemic inflammation during pregnancy and postnatal neonatal inflammatory exposure enhance ROP pathogenic risk. Maternal gestational inflammation primarily

manifests through histological chorioamnionitis, whereas postnatal inflammation primarily results from neonatal sepsis (17). Histological chorioamnionitis represents a prevalent perinatal inflammatory condition reflecting maternal immune response to chorioamniotic bacterial infection of chorionic villi and placental membranes. Sepsis constitutes a systemic inflammatory response syndrome (SIRS) induced by infection with diverse pathogens. Through a meta-analysis, Wang *et al* (18) concluded that sepsis demonstrates a strong association with ROP at all disease stages, particularly severe ROP, substantially elevating ROP risk in preterm populations. Animal model investigations demonstrated that early severe SIRS precipitates abnormal retinal vascular development with increased vascular anastomosis associated with microglial activation (19).

Additionally, vascular endothelial damage from pathogenic organisms and their toxins promotes leukocyte adherence to vessel walls with microthrombus formation in small retinal vessels, leading to vascular obstruction and leakage. N represents the most direct inflammation indicator, with retrospective case-control investigation demonstrating elevated first-month N in preterm infants with ROP compared with that in no-ROP counterparts (20). The present investigation identified significantly elevated sepsis incidence in the ROP group compared with that in the no-ROP group. Comprehensive inflammatory indices, including NLR, PLR, LMR and SII, provide more comprehensive immune assessment compared with isolated leukocyte components, bearing substantial diagnostic and prognostic relevance for infectious and non-infectious conditions. These composite indices have emerged as potential inflammatory markers for diverse disease diagnosis and prognosis, demonstrating association with classical inflammatory mediators, including C-reactive protein, IL-6 and TNF- α , while offering advantages such as superior accessibility, elimination of additional examination costs and superior stability compared with conventional biomarkers. Recent investigations have examined associations between these novel markers and ROP, although limited foreign literature currently addresses SII-ROP relationships (20). Complete blood count analysis at 1-week in preterm infants identified elevated NLR in ROP-affected children compared with no-ROP counterparts, with independent NLR association with ROP development (20). Through retrospective evaluation of preterm infants with GA <35 weeks at birth and at 1-month follow-up, Akdogan *et al* (20) identified significant differences in LMR between the no-ROP and ROP groups both at birth and at 1 month of age, with elevated LMR in ROP-affected infants. The present study identified higher LMR in the no-ROP group compared with that in the ROP group, leading to the hypothesis that elevated LMR represents a ROP protective factor. At 1 week of age, the current investigation identified significantly elevated NLR in the no-ROP vs. ROP group, with PLR demonstrating no ROP association, which was possibly attributable to limited control sample collection. Through a retrospective analysis, Kiran *et al* (21) identified no association between NLR or PLR (at 24 h of age) and ROP, and no association with the requirement for ROP treatment, possibly as blood samples were obtained within 24 h of birth when immature neonatal immune systems affect results. These discordant findings

regarding the association between ROP and comprehensive inflammatory indices may relate to the timing variability of blood specimen collection.

Platelets are cytoplasmic fragments produced by megakaryocyte fragmentation lacking cell nuclei, possessing active physiological properties that regulate neovascularization and fibrin formation and deposition. Research has demonstrated that platelets can locally promote or inhibit angiogenesis. Platelets contain α -granules storing diverse angiogenic regulators, including pro-angiogenic factors (such as VEGF and IGF-1) and anti-angiogenic factors (such as endothelial inhibitors), stored in distinct granules and released selectively, thus regulating angiogenesis (21). MPV quantifies platelet volume and size, reflecting platelet activity status. Larger platelets demonstrate elevated metabolic and enzymatic activity with increased α -granule content; when stimulated by hypoxia, platelets exhibit hyperfunction with increased mean size. Larger platelets release greater quantities of pro-angiogenic factors, thus promoting neovascularization formation (22,23). Consequently, platelets substantially influence angiogenesis regulation. Investigations have demonstrated a correlation between decreased PLT and ROP development (24,25). Retrospective studies categorizing preterm infants into no-ROP, mild ROP (treatment-naïve) and severe ROP (treatment-requiring) groups identified low first-week PLT as an ROP development risk factor. The literature suggests that platelets scavenge VEGF, thus regulating neovascularization; when platelets decrease, VEGF scavenging diminishes, leading to elevated VEGF and massive neovascularization (21). These findings suggest that lower PLT increase preterm infant ROP risk. However, other investigations identified no association between lower PLT and ROP. Through retrospective analysis, Cakir *et al* (24) identified no notable PLT difference between children with treatment-requiring and treatment-naïve ROP, possibly since the study failed to exclude platelet transfusion frequency or thrombocytopenia duration effects on ROP, as platelet transfusions reduce VEGFA protein expression, thereby decreasing ROP development (25,26). In a prospective cohort investigation, Reddy *et al* (27) similarly identified no association between PLT and ROP, possibly since higher Neonatal Intensive Care Unit care levels and improved neonatal overall health prevented ROP development and the study inadequately controlled for neonatal sepsis bias (27). In the present study, children in the ROP group demonstrated significantly lower PLT compared with the no-ROP group both at 24 h and 1 week after birth; consequently, thrombocytopenia is considered a risk factor for ROP development. The present study identified that at 1 week of age, ROP-affected children demonstrated significantly elevated MPV compared with children in the no-ROP group. We hypothesize that MPV is an ROP occurrence risk factor and that this reflects the retinal hypoxic state in ROP at this timepoint, with sustained VEGF expression elevation stimulating extensive neovessel formation wherein platelets regulate neovascularization and transport neovascularization-generating factors. Peripheral blood platelets demonstrate hyperfunction with increased volume, yielding relatively elevated MPV values. Currently, limited domestic and international literature addresses the correlation between the platelet parameter and ROP, and

the effects of platelets on VEGF balance, ROP severity and pathogenesis warrant further investigation.

Reduced Hb content results in diminished oxygen-carrying capacity. Through retrospective analysis of complete blood count parameters in 150 preterm neonates, Akyüz Ünsal *et al* (28) identified mean corpuscular Hb (MCH) as the most significant parameter predictor compared with other blood count indices, including mean erythrocyte volume and platelet distribution width. MCH represents the mean Hb value within erythrocytes; the study proposed that the mechanistic relationship between MCH and ROP may involve the nitric oxide (NO) pathway, wherein excess NO induces vasodilatation, capillary leakage and edema, while Hb scavenges NO generating Hb-NO complexes. These investigations underscore the importance of adequate Hb for ROP prevention. The present study identified that lower 1-week Hb in preterm infants represents an ROP development risk factor, with blood transfusion also constituting an ROP development risk factor. Adult Hb (HbA) transfusion increases neonatal ROP risk, as HbA demonstrates lower oxygen affinity than fetal Hb, and HbA shifts the oxygen dissociation curve to the right, increasing dissolved plasma oxygen proportion and elevated tissue oxygen exposure (29-31). Additionally, sudden post-transfusion blood free iron elevation can generate Fenton reactions producing free hydroxyl radicals causing retinal damage and inducing retinopathy (32). Early anemia correction can effectively reduce severe ROP lesion incidence and provide favorable conditions for ROP spontaneous regression; nevertheless, large-scale prospective investigations remain necessary to assess the predictive value of early anemia recognition for ROP in preterm infants. While our previous ROP-only analysis found no association between maternal ApoA1 and disease severity (2), the present study demonstrates that reduced maternal ApoA1 significantly predicts ROP occurrence. This dissociation suggests that maternal lipid metabolism may influence disease initiation, whereas post-natal factors drive progression. As the two studies employ mutually exclusive control groups (ROP-free vs. mild ROP), they address non-overlapping scientific questions.

Limited investigations have examined the effects of dyslipidemia on ROP pathogenesis. Yang *et al* (33), employing mass spectrometry to investigate the role of metabolic alterations in ROP development, identified notable plasma metabolic disturbances in ROP-affected vs. no-ROP groups, including elevated lipid levels and hyperactive lipid metabolism (30). The retina exhibits a substantial lipid content, with lipid oxidation constituting a major retinal energy source, and dyslipidemia can modulate pathological retinal angiogenesis. Dyslipidemia manifests through elevated serum TC, LDL and TG levels, or decreased serum HDL concentrations. The present investigation identified reduced maternal third-trimester ApoA1 as an influential factor in ROP development; multivariate logistic regression analysis results revealed that reduced maternal third-trimester ApoA1 was an independent ROP development risk factor, and ROC curve analysis established reduced ApoA1 as early ROP development predictor. Lipid metabolism disorders may relate to adiponectin (APN), an endogenous bioactive protein secreted by adipocytes that regulates glucose and lipid metabolism (34). APN regulates lipid metabolism primarily

through two pathways: Promoting fatty acid oxidation and inhibiting lipid synthesis, thereby reducing circulating TG or cholesterol levels. The literature demonstrates that adiponectin concentrations are lower in ROP-affected preterm infants compared with those in no-ROP counterparts. Adiponectin may inhibit neovascularization through regulation of serum TNF- α , IGF-1, omega-3 long-chain polyunsaturated fatty acids and VEGF levels, thereby inhibiting ROP onset and progression. In clinical practice, attention to preterm infant and maternal late-pregnancy lipid profiles, particularly reduced ApoA1 levels, facilitates the prediction of ROP occurrence (35).

The present study acknowledges several important limitations requiring discussion. The retrospective design may introduce selection bias associated with single-center data collection (n=102). The modest sample size resulted in limited statistical power, particularly with insufficient control group representation (only 22 cases), and potential confounding factors such as intrauterine infection were not definitively excluded. We acknowledge that the present study shares a data source with our previously published severity-stratified analysis; however, the two studies employ analytically distinct contrasts and control groups. Future multicenter prospective investigations will be required to validate the ApoA1 threshold.

In conclusion, the present study demonstrated that reduced maternal third-trimester ApoA1 is an independent risk factor for ROP, and that a maternal ApoA1 level <0.584 g/l predicted ROP with 90.9% sensitivity and 67.5% specificity (AUC, 0.768), supporting its value as an early maternal biomarker for ROP risk stratification. ApoA1, the principal protein component of HDL, exerts established anti-inflammatory effects through the inhibition of NF- κ B activation and the reduction of TNF- α and IL-6 production (36). The present cohort concluded that reduced maternal ApoA1 is a risk factor for ROP, suggesting that this association may not be mediated through conventional anti-inflammatory pathways alone. Maternal lipid metabolism and lipoprotein profiles influence substrate availability for fetal development through placental lipid transfer (37). APN inhibits VEGF-stimulated angiogenesis and attenuates pathological retinal neovascularization in ischemic retinopathy models (38), and reduced APN levels have been observed in preterm infants with ROP (34). Whether reduced maternal ApoA1 reflects altered HDL function affecting maternal-fetal lipid signaling or adiponectin-VEGF axis regulation remains to be determined. The mechanistic link between maternal ApoA1 and fetal retinal vascular development requires direct investigation in prospective studies.

While the logistic regression model successfully identified independent risk factors, the generalizability of the findings requires further validation given the limitations of a single-center retrospective design with a modest sample size (n=102). Future studies utilizing larger multicenter cohorts will be essential to confirm the predictive stability of ApoA1 as a biomarker for ROP risk stratification.

Acknowledgements

We appreciate the support and assistance from Roche Pharma China and the Roche Ophthalmology Academy.

Funding

The present study was supported by the Hebei Province Medical Applicable Technology Tracking Project (grant no. GZ2020094).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QM and XL were responsible for study conception and design, data acquisition, analysis and interpretation, and drafting of the manuscript. JW performed the statistical analysis and was responsible for figure preparation and critical revision for intellectual content. KL and WT were responsible for patient recruitment, data collection and technical support. FF, HZ, KL and WT also responsible for data analysis. QM, XL, FF and HZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of Hebei General Hospital [ethics approval no. 115 (2024)]. Due to the retrospective nature of the present study utilizing existing medical records, the Ethics Committee waived the requirement for informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Xu S, Liang Z, Du Q, Li Z, Tan G, Nie C, Yang Y, Lv X, Zhang C and Luo X: A systematic study on the prevention and treatment of retinopathy of prematurity in China. *BMC Ophthalmol* 18: 44, 2018.
2. Dammann O, Hartnett ME and Stahl A: Retinopathy of prematurity. *Dev Med Child Neurol* 65: 625-631, 2023.
3. Ma Q, Lv X, Wang J, Li K and Tang W: Risk factors for severe retinopathy of prematurity: A retrospective case-control study. *Exp Ther Med* 31: 143, 2026.
4. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, Binenbaum G, Blair M, Peter Campbell J, Capone A Jr, *et al*: International classification of retinopathy of prematurity, third edition. *Ophthalmology* 128: e51-e68, 2021.
5. Hu X, Zhang J, Zhang M, Chen X, Han S and Zhu J: Incidence and risk factors for retinopathy of prematurity in a tertiary hospital in China. *Clin Ophthalmol* 17: 3189-3194, 2023.
6. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP and Chiang MF: Retinopathy of prematurity: A review of risk factors and their clinical significance. *Surv Ophthalmol* 63: 618-637, 2018.
7. Gestational Hypertension and Preeclampsia: ACOG practice bulletin No. 222. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 135: e237-e260, 2020.

8. Zeisler H, Llubra E, Chantraine F, Vatish M, Staff AC, Sennström M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, *et al*: Predictive value of the sFlt-1:PIGF ratio in women with suspected preeclampsia. *N Engl J Med* 374: 13-22, 2016.
9. Verlohren S, Brennecke SP, Galindo A, Karumanchi SA, Mirkovic LB, Schlembach D, Stepan H, Vatish M, Zeisler H and Rana S: Clinical interpretation and implementation of the sFlt-1/PIGF ratio in the prediction, diagnosis and management of preeclampsia. *Pregnancy Hypertens* 27: 42-50, 2022.
10. Miller JJ, Higgins V, Melamed N, Hladunewich M, Ma L, Yip PM and Fu L: Clinical validation of the sFlt-1:PIGF ratio as a biomarker for preeclampsia diagnosis in a high-risk obstetrics unit. *J Appl Lab Med* 8: 457-468, 2023.
11. Yu XD, Branch DW, Karumanchi SA and Zhang J: Preeclampsia and retinopathy of prematurity in preterm births. *Pediatrics* 130: e101-e107, 2012.
12. Chan PYL, Tang SM, Au SCL, Rong SS, Lau HHW, Ko STC, Ng DSC, Chen LJ and Yam JCS: Association of gestational hypertensive disorders with retinopathy of prematurity: A systematic review and meta-analysis. *Sci Rep* 6: 30732, 2016.
13. Opara CN, Akintorin M, Byrd A, Cirignani N, Akintorin S and Soyemi K: Maternal diabetes mellitus as an independent risk factor for clinically significant retinopathy of prematurity severity in neonates less than 1500g. *PLoS One* 15: e0236639, 2020.
14. Ali YF, El-Morshedy S, Imam AA, Abdelrahman NIA, Elsayed RM, Alkholi UM, Abdalmonem N and Shehab MM: The role of serum apelin in retinopathy of prematurity. *Clin Ophthalmol* 11: 387-392, 2017.
15. Marinov VG, Koleva-Georgieva DN, Sivkova NP and Krasteva MB: The 5-minute apgar score as a prognostic factor for development and progression of retinopathy of prematurity. *Folia Med (Plovdiv)* 59: 78-83, 2017.
16. Podraza W, Michalczyk B, Jezierska K, Domek H, Kordek A, Łoniewska B, Modrzejewska M and Kot J: Correlation of retinopathy of prematurity with bronchopulmonary dysplasia. *Open Med (Wars)* 13: 67-73, 2018.
17. Lin YW, Chen SN, Muo CH, Sung FC and Lin MH: Risk of retinopathy of prematurity in preterm births with respiratory distress syndrome: A population-based cohort study in Taiwan. *Int J Gen Med* 15: 2149-2162, 2022.
18. Wang X, Tang K, Chen L, Cheng S and Xu H: Association between sepsis and retinopathy of prematurity: A systematic review and meta-analysis. *BMJ Open* 9: e025440, 2019.
19. Tremblay S, Miloudi K, Chaychi S, Favret S, Binet F, Polosa A, Lachapelle P, Chemtob S and Sapieha P: Systemic inflammation perturbs developmental retinal angiogenesis and neuroretinal function. *Invest Ophthalmol Vis Sci* 54: 8125-8139, 2013.
20. Akdogan M, Ustundag Y, Cevik SG, Dogan P and Dogan N: Correlation between systemic immune-inflammation index and routine hemogram-related inflammatory markers in the prognosis of retinopathy of prematurity. *Indian J Ophthalmol* 69: 2182-2187, 2021.
21. Kıran Yenice E, Kara C, Karslı Türkoglu T, Ulubaş Işık D and Çelik İH: Predictive value of serum inflammatory markers in retinopathy of prematurity. *Eye (Lond)* 38: 2822-2826, 2024.
22. Parrozzani R, Nacci EB, Bini S, Marchione G, Salvadori S, Nardo D and Midena E: Severe retinopathy of prematurity is associated with early post-natal low platelet count. *Sci Rep* 11: 891, 2021.
23. Yolcu U and Civan DY: Relationship between mean platelet volume and retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol* 253: 2337, 2015.
24. Cakir B, Liegl R, Hellgren G, Lundgren P, Sun Y, Klevebro S, Löfqvist C, Mannheimer C, Cho S, Poblete A, *et al*: Thrombocytopenia is associated with severe retinopathy of prematurity. *JCI Insight* 3: e99448, 2018.
25. Şahinoğlu Keşkek N, Gülcan H, Yılmaz G and Akkoyun İ: Impact of platelet count in retinopathy of prematurity. *Türk J Ophthalmol* 50: 351-355, 2020.
26. Oztürk T, Durmaz Engin C, Kaya M and Yaman A: Complete blood count parameters to predict retinopathy of prematurity: When to evaluate and what do they tell us? *Int Ophthalmol* 41: 2009-2018, 2021.
27. Reddy RM, Bhandary SV, Rao KA, Lewis LE, Lal SM and Rachel NM: Assessment of role of platelet indices in the occurrence of retinopathy of prematurity. *Middle East Afr J Ophthalmol* 29: 91-95, 2023.
28. Akyüz Ünsal A, Key Ö, Güler D, Kurt Omurlu İ, Anık A, Demirci B and Dündar S: Can complete blood count parameters predict retinopathy of prematurity? *Türk J Ophthalmol* 50: 87-93, 2020.
29. Teofili L, Bianchi M, Baldascino A, Papacci P and Vento G: Foetal haemoglobin, blood transfusion, and retinopathy of prematurity. *Eye (Lond)* 32: 1155-1156, 2018.
30. Erdöl H, Hacıoğlu D, Kola M, Türk A and Aslan Y: Investigation of the effect of hemoglobin F and A levels on development of retinopathy of prematurity. *J AAPOS* 21: 136-140, 2017.
31. Prasad N, Kumar K and Dubey A: Fetal hemoglobin, blood transfusion, and retinopathy of prematurity in preterm infants: An observational, prospective study. *Indian J Ophthalmol* 71: 2803-2807, 2023.
32. Dai AI, Demiryürek S, Aksoy SN, Perk P, Saygili O and Güngör K: Maternal iron deficiency anemia as a risk factor for the development of retinopathy of prematurity. *Pediatr Neurol* 53: 146-150, 2015.
33. Yang Y, Yang Q, Luo S, Zhang Y, Lian C, He H, Zeng J and Zhang G: Comparative analysis reveals novel changes in plasma metabolites and metabolomic networks of infants with retinopathy of prematurity. *Invest Ophthalmol Vis Sci* 63: 28, 2022.
34. Fu Z, Löfqvist CA, Shao Z, Sun Y, Joyal JS, Hurst CG, Cui RZ, Evans LP, Tian K, SanGiovanni JP, *et al*: Dietary ω -3 polyunsaturated fatty acids decrease retinal neovascularization by adipose-endoplasmic reticulum stress reduction to increase adiponectin. *Am J Clin Nutr* 101: 879-888, 2015.
35. Fu Z, Gong Y, Löfqvist C, Hellström A and Smith LEH: Review: Adiponectin in retinopathy. *Biochim Biophys Acta* 1862: 1392-1400, 2016.
36. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M and Fogelman AM: Antiinflammatory properties of HDL. *Circ Res* 95: 764-772, 2004.
37. Herrera E, Amusquivar E, López-Soldado I and Ortega H: Maternal lipid metabolism and placental lipid transfer. *Horm Res* 65 (Suppl 3): S59-S64, 2006.
38. Bora PS, Kaliappan S, Lyzogubov VV, Tytarenko RG, Thotakura S, Viswanathan T and Bora NS: Expression of adiponectin in choroidal tissue and inhibition of laser induced choroidal neovascularization by adiponectin. *FEBS Lett* 581: 1977-1982, 2007.



Copyright © 2026 Ma *et al*. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.