Progress in the study of association between hematological indicators and retinopathy of prematurity (Review)

WENWEN TANG[1], YIN ZHANG[1], HAIFANG ZHANG[1], KEJUN LI[1], ZHIHUA ZHAO[1], HUIJIE MA[2], XINLI JIANG[3], ZHIYANG JIA[1] and QINGMIN MA[1]

[1]Department of Ophthalmology, Hebei General Hospital, Shijiazhuang, Hebei 050051, P.R. China; [2]Department of Physiology, Hebei Medical University, Shijiazhuang, Hebei 050017, P.R. China; [3]Department of Ophthalmology, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei 050051, P.R. China

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Abstract. Retinopathy of prematurity (ROP) is a retinopathy caused by abnormal proliferation of blood vessels in premature infants. It can lead to retinal detachment and, in severe cases, blindness, rendering ROP a critical condition. Advances in neonatal medicine have improved survival rates of low birth weight and low gestational age infants. However, this progress has also led to a rise in incidence of ROP. Currently, premature birth, low birth weight and high postpartum oxygen levels are independent risk factors for ROP. Other factors include mode of delivery, multiple births, anemia, blood transfusion, maternal pregnancy factors, neonatal bronchopulmonary dysplasia, use of surfactants, arterial ductus arteriosus and necrotizing enterocolitis. Laboratory indicators in premature infants such as platelet count, levels of blood glucose, inflammatory cells, lipid and hemoglobin and blood transfusion may also be associated with ROP. However, the etiology and pathogenesis of ROP are not fully understood. A number of factors may influence the onset and progression of ROP, including decreased platelet counts, decreased hemoglobin levels, increased white blood cell counts, increased blood glucose levels, and disorders of lipid metabolism. The present study reviewed the effects of platelet count, hemoglobin, blood glucose, inflammatory cells and factors, blood lipids, and plasma metabolic pathways on ROP.

Contents

Correspondence to: Professor Qingmin Ma, Department of Ophthalmology, Hebei General Hospital, 348 West Heping Road, Shijiazhuang, Hebei 050051, P.R. China
E-mail: min7409-2002@foxmail.com

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1. Introduction

Retinopathy of prematurity (ROP) is a vascular abnormal proliferative retinopathy in premature infants. ROP is preventable and treatable; early screening enables timely implementation of optimal therapeutic interventions for affected premature infants. The World Health Organization Vision 2020 project identified ROP as the leading cause of childhood blindness (1,2). Advances in neonatal medicine have markedly decreased the rate of preterm births worldwide; an artificial intelligence-based epidemiological assessment in India showed that the proportion of infants with moderate to severe ROP has significantly decreased over two time periods (August 2015 to October 2017 and March 2019 to December 2020) in South India (3). However, the incidence of ROP-associated blindness is increasing worldwide, particularly in low- and middle-income countries. Despite improved conditions and facilities in neonatal intensive care units (NICUs) in low- and middle-income countries, many NICUs need more resources and equipment to monitor and prevent ROP. It is estimated that ~50,000 children worldwide are permanently blinded by ROP each year, 4,000 of which are in China; China accounts for 1.9% of all children under the age of five who become blind due to ROP globally (4,5). Therefore, it is key to study the pathogenesis and influencing factors of ROP. Several factors affect development of ROP, however pathogenesis and risk factors for ROP are not fully understood. In addition to preterm birth, low birth weight and high postnatal oxygen uptake, which have been recognized as risk factors worldwide, other factors include mode of delivery, multiple births, maternal pregnancy factors, neonatal bronchopulmonary dysplasia, use of surfactants, arterial duct inactivity, necrotizing enterocolitis, race and Apgar scores (6). In recent years, several hematological indicators have been suggested to influence the development and clinical course of ROP (7-11). The present review summarizes the impact of hematological indicators on ROP.

2. Pathogenesis of ROP

Fetal retinal vascularization begins at 16 weeks gestation and reaches the nasal ora serrata at ~36 weeks gestation. By contrast, the temporal ora serrata is not fully vascularized until ~40 weeks of corrected gestational age. Therefore, retinal blood vessels in preterm infants are not yet fully developed and need to continue to develop after birth. It is hypothesized that the pathogenesis of ROP is mainly due to an imbalance between pro- and antiangiogenic factors. Vascular endothelial growth factor (VEGF) is involved in the development of ROP. VEGF is a family of polypeptides that exerts its effects primarily through binding to tyrosine kinase receptors, which play an essential role in ROP. The expression of VEGF in humans is closely associated with blood oxygen saturation (SpO_2), with hypoxia upregulating VEGF and hyperoxia downregulating VEGF (12). Studies have shown that the pathogenesis of ROP is divided into two phases (12,13). Phase I is characterized by vaso-obliteration, which commences at premature birth as premature infants are born into a relatively hyperoxic environment [the partial pressure of oxygen (PaO_2) in the extra-uterine environment is close to 100 mmHg, whereas PaO_2 is <35 mmHg *in utero*]; hyperoxia inhibits VEGF production and the sudden decrease in VEGF disrupts normal retinal development. Phase II is characterized by vaso-proliferation. During this phase, disrupted vascular development results in insufficient blood supply to the retina, a consequence of its gradual maturation. This insufficiency leads to retinal hypoxia, which increases VEGF expression. If the avascular region is minimal, heightened VEGF levels can promote blood vessel growth to finalize retinal vascularization, meaning ROP can resolve spontaneously. When avascularity is extensive, VEGF prompts neovascularization in the retina. Furthermore, insulin-like growth factor (IGF)-1 collaborates with VEGF to modulate this neovascularization process (13,14). An overproduction or disproportion of these elements can result in ROP (12-14).

The pathogenesis of ROP is associated with reactive oxygen species (ROS) and nitric oxide synthase (NOS) (15). Premature infants are exposed to relatively high oxygen levels after birth and have an underdeveloped antioxidant system. This leads to excessive production of ROS, triggering the oxidative stress-related signaling pathways, which causes apoptosis in endothelial cells. This leads to retinal vascular occlusion that disrupts the development of normal retinal blood vessels. NOS, an isoenzyme located in neuronal cells, neurophagocytes, macrophages and endothelial cells, exists in three isoforms: Neuronal, inducible and endothelial-type NOS (eNOS). In hyperoxia, eNOS-derived NO participates in the superoxide reaction to form peroxynitrite ($ONOO^-$), an essential mediator of hyperoxia-induced vascular occlusion. Hypoxia induces activation of NOS, activates the JAK/STAT3 pathway and mediates neovascularization. In addition, hypoxia induces an increase in VEGF expression, which activates eNOS through the Akt signaling pathway (15,16). The NO produced by eNOS impairs integrity of vascular endothelial cell adhesion junctions, leading to enhanced vascular permeability. In addition, NO serves as a vasodilator and exhibits anti-occlusive and proangiogenic properties. Under normal oxygen levels, hypoxia-inducible factor-1α (HIF-1α) is hydroxylated in the cytoplasm by the prolyl hydroxylase structural domain (PHD). Both oxygen and iron serve as essential cofactors for PHD, and hypoxia inhibits PHD enzyme activity, which increases the stability and levels of HIF-1α, subsequently elevating VEGF production. Conversely, hyperoxia inhibits HIF-1α, resulting in a decrease in VEGF and vascular occlusion. In summary, stage I of ROP is associated with increased ROS and $ONOO^-$ and decreased levels of VEGF and HIF-1α, whereas stage II is associated with the activation of eNOS and increased levels of HIF-1α and VEGF (Fig. 1) (15,17). Retinal detachment occurs in severe cases of ROP, leading to permanent blindness. However, if existing blood vessels continue to grow normally and complete peripapillary retinal vascularization, ROP may be healed spontaneously (15).

3. Effect of hematological indicators on ROP

In recent years, an increasing number of studies (7-11) have revealed that various laboratory markers in children, including hemoglobin (Hb), platelet count, blood glucose (BG) and inflammatory cells, may be linked to the development of ROP (Table I). These findings demonstrate the etiology of ROP and its association with systemic reactions. Hematological indicators may be used as indicators of risk factors and prognosis outcomes for ROP.

Effect of platelets (PLTs) on ROP. The role of PLTs in ROP is not yet fully understood. PLTs are cytoplasmic clumps without nuclei produced by megakaryocytes and have active physiological properties that regulate neovascularization, fibrin formation and deposition (18,19). Studies (19-22) have shown that PLTs locally promote or inhibit angiogenesis. Platelets contain granules that store regulators of angiogenesis, including VEGF and angiogenesis inhibitors (such as endothelial inhibitors), which are released, thus regulating angiogenesis (23). Most studies (24,25) have shown that a reduced PLT count is associated with ROP. Cakir *et al* (18) discovered that thrombocytopenia at the corrected gestational age of >30 weeks is independently associated with severe ROP that requires treatment. In addition, they found that low PLT count during the neovascularization phase of ROP (phase II) is significantly associated with development of severe ROP.

Şahinoğlu *et al* (25) also found that a low PLT count is independently associated with severe ROP. Therefore, low PLT count may increase the risk of ROP in preterm infants. Parrozzani *et al* (23) demonstrated that PLTs act as scavengers in neovascularization by clearing VEGF. A decrease in PLT count results in reduced VEGF elimination, leading to an increase in VEGF and subsequent massive neovascularization. Most studies (21,23,26) have found an association between thrombocytopenia and development or severity of ROP; however, a few studies (7,27) detected no association between low PLT levels and ROP. Choręziak *et al* (27) found no difference in the early postnatal PLT count between patients with ROP that do and do not require treatment. However, a decrease in PLT count before the diagnosis of ROP is key for the development of ROP. This may be attributed to the immaturity of the blood system at birth. A retrospective study by Özkaya (7) showed no significant difference in PLT between children with ROP requiring treatment and those not requiring treatment.

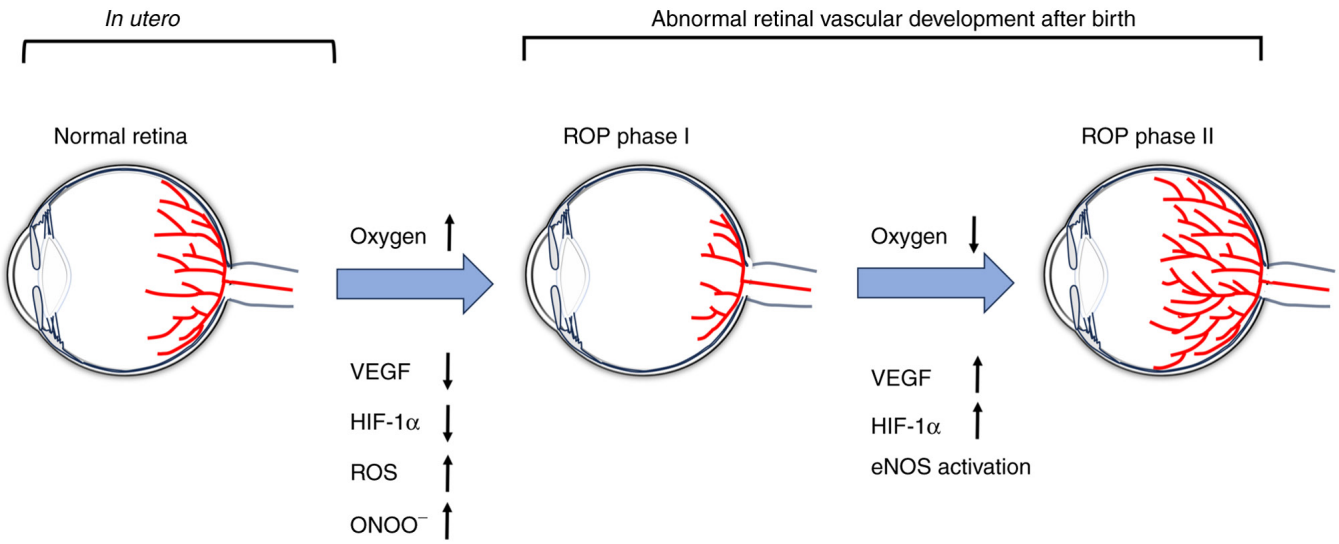

Figure 1. ROP stages and the changes in cytokines at different phases. Phase I is associated with increased ROS and $ONOO^-$ and decreased levels of VEGF and HIF-1α, whereas phase II is associated with the activation of eNOS and increased levels of HIF-1α and VEGF. ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor; HIF-1α, hypoxia-inducible factor-1α; ROS, reactive oxygen species; eNOS, endothelial-type nitric oxide synthase.

However, the number of children with thrombocytopenia (PLT count <150x10^9/l) was higher in the group that needed treatment compared with the group that did not. This may be because the study did not exclude subjects based on number of PLT transfusions or the duration of thrombocytopenia. Lim *et al* (19) studied mean weekly PLT during the first 6 weeks of life. After adjusting for covariates, there was no significant difference between mean PLT count of preterm infants in the group with ROP and without ROP. Decreased PLT count is not directly linked to ROP, but an effect of other risk factors such as sepsis, blood transfusion and bronchopulmonary dysplasia (19). ROP is influenced by various factors and due to different research and statistical methods, the results can also vary. Recent research (22) examining the impact of stage I and II PLT parameters on ROP has shown no differences in stage I platelet parameters. However, an increase in PLT in stage II with more VEGF release results in increased neovascularization, which contradicts the findings of Parrozzani *et al* (23). Therefore, the effect of increased or decreased PLT count on ROP is inconclusive, and the pathological mechanisms of PLT count on ROP need further study.

An association has been found between mean PLT volume (MPV) and ROP. MPV reflects PLT size and activity and is a marker of PLT reactivity. During the second stage of ROP, the retina is in a state of hypoxia. The continued increase in VEGF expression stimulates formation of multiple new blood vessels, in which PLTs serve a role in regulating neovascularization and transporting neovascularization factors (28). PLTs in peripheral blood are hyperfunctional, large in size and have a relatively high MPV (28,29). Clinical studies (20,29) have shown a statistically significant difference in MPV levels between children with ROP and controls. Increase in MPV volume raises the risk of ROP by a factor of 1.94 (29). MPV levels are associated with diabetic retinopathy, suggesting a link between activated PLTs and proliferative retinopathy (30,31). To the best of our knowledge, there is a lack of research on the association between PLT parameters and ROP; effect of PLTs on VEGF homeostasis and the severity and pathogenesis of ROP requires further investigation.

Effect of Hb, post-transfusion adult Hb (HbA) and fetal Hb (HbF) on ROP

Effect of Hb on ROP. Reduced Hb levels result in less oxygen being transported. At stage I of ROP, infants with lower Hb levels are unable to meet the increased oxygen demand of the developing retina and retinal vascularization is delayed. At stage II, hypoxia increases VEGF levels, thereby promoting neovascularization (32). Lundgren *et al* (33) conducted a retrospective study of 227 preterm infants aged ≤28 weeks. Hb levels in the first week of life were significantly lower in infants with ROP requiring treatment than those not requiring treatment. Logistic regression analysis demonstrated the duration of anemia in the first week of life in infants with ROP requiring treatment is an independent risk factor for ROP treatment. Therefore, early prevention of anemia decreases risk of developing ROP. Akyüz *et al* (34) retrospectively analyzed complete blood count (CBC) parameters in 150 preterm infants; mean corpuscular Hb (MCH) of erythrocytes was the most significant predictor among all parameters. MCH represents the average value of Hb in erythrocytes. The association between MCH and ROP may be associated with the NO pathway. Excess NO can cause vasodilation, capillary leakage and edema, while Hb scavenges NO, resulting in the formation of Hb-NO complexes (34). The aforementioned studies indicate the importance of sufficient Hb in preventing ROP.

Effect of HbA and HbF on ROP after transfusion. HbF serves as the primary oxygen transport protein during fetal development and is involved in transporting oxygen from maternal blood to fetal organs and tissue. In preterm infants, HbF is converted to HbA after birth. HbF has a higher oxygen affinity than HbA. The oxygen dissociation curve of HbF is shifted to the left compared with HbA, thus HbF has a higher oxygen affinity than HbA at any oxygen partial pressure (32).

Table I. Association of hematological indicators with ROP and possible pathophysiological mechanisms.

Biochemical index	Potential mechanisms	Research indicators	Association with ROP	(Refs.)
Blood PLT	Granules in PLTs store angiogenic regulatory factors	PLT count	Negative	(18,25)
			None	(7,19,27)
		MPV	Positive (phase II)	(20,29)
Hb	Lower levels result in less oxygen being carried	Hb	Negative	(33,34)
Post-transfusion Hb	Shift in the oxygen dissociation curve caused by replacement of HbF by HbA results in a higher proportion of dissolved oxygen in plasma	HbF	Negative	(8,32)
		HbA	Positive	(8,32)
Blood GLU	Hyperglycemia stimulates VEGF production via activation of protein kinase C	GLU	Positive	(41)
			None	(47)
		HbA1C	Negative (non-proliferative ROP)	(49)
			Positive (proliferative ROP)	(49)
Inflammation	Inflammation activates microglia; infection and inflammation damage vascular endothelium; retinal perfusion is compromised in infected infants due to hypotension and changes in oxygenation levels	NEUT (chorioamnionitis, sepsis)	Positive	(31,51, 52,56)
		NLR	Positive	(10)
			None	(60)
		PLR	None	(60)
		SII	Positive	(56)
		CAR	Positive	(65)
		IL-6, IL-8	Positive	(66,67, 68,73)
Blood lipids	Retina is rich in lipids and lipid oxidation is a key source of energy for the retina; dyslipidemia can affect pathological angiogenesis in the retina and inhibit neovascularization by regulating serum levels of VEGF	Total cholesterol, LDL, triglycerides	Positive	(11)
		Lipocalin	Negative	(75,76)

ROP, retinopathy of prematurity; PLT, platelet; MPV, mean platelet volume; HbF, fetal hemoglobin; HbA, adult hemoglobin; GLU, glucose; HbA1C, glycated hemoglobin; NEUT, neutrophil; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic inflammatory response syndrome; CAR, C-reactive protein/albumin ratio; LDL, low density lipoprotein.

The substitution of HbF for HbA causes the oxygen dissociation curve to shift left, leading to a higher proportion of dissolved oxygen in plasma and an increase in tissue exposure to oxygen (8,35). Studies have shown that low levels of HbF are independently associated with development of ROP and that maintaining higher levels of HbF may protect against ROP (8,32). Therefore, different transfusion regimens may affect outcome of ROP. Children with anemia who receive transfusions of adult red blood cells have a higher incidence of ROP compared with those who receive transfusions of autologous cord blood red cells. In addition, an association is found between the number of blood transfusions and ROP (36). A study suggests that performing ≥3 transfusions before 32 weeks gestation raises risk of ROP (37). The substitution of HbF with HbA during transfusion could contribute to the progression of ROP (38). In a prospective cohort study, Stutchfield *et al* (39) found a negative association between mean Hb concentration and severity of ROP in postnatal fetuses. They also found that replacing HbF with HbA during transfusion accelerates the development of ROP. This is because transfusing infants with HbA can suddenly deliver a large amount of oxygen to the retina, which downregulates VEGF and leads to stagnation in the development of the retinal vasculature. It has also been suggested that the sudden increase in free iron in blood following the transfusion of adult blood may induce the Fenton reaction, which generates free hydroxyl radicals that damage the retina, thereby inducing retinopathy (40). Moderate blood transfusions are administered to raise Hb levels, which increases oxygen concentration and decreases hypoxic damage to the body. However, excessive adult blood transfusions increase the risk of ROP (39). Therefore, studies in preterm neonates have highlighted that a balance must be found between toxic effects of high-oxygen saturation and the damage caused by hypoxia; during transfusion, it is essential to monitor blood oxygen saturation to prevent anemia and potential damage to the retina from excessive transfusion (16,39).

Therefore, prospective research is required to evaluate the predictive value of early anemia detection in preterm infants for ROP.

Influence of glycaemia on ROP. Elevated BG causes biological changes in the retina and most studies (41,42) have found a positive association between BG levels and development of ROP. Mohsen *et al* (41) conducted a prospective study of 65 children to investigate the association between BG and ROP. They found that maximum and mean BG concentrations were significantly higher in children with than those without ROP. Using logistic regression analysis, they concluded that increase in mean BG concentration in the first week of life is an independent risk factor for developing ROP, which was in accordance with the findings of Vannadil *et al* (42). In studies (43,44) on the mechanisms by which elevated BG levels affect ROP, it has been found that BG levels are primarily associated with VEGF and IGF-1 and act synergistically. VEGF protein expression in cultured retinal Müller cells is increased at higher glucose concentrations (45), as hyperglycemia can stimulate VEGF production by activating protein kinase C (46). Low serum levels of IGF-1 promote pathological neovascularization in the retina. Studies (43,42) have shown that low levels of IGF-1 inhibit development of normal retinal vasculature, leading to local ischemia and the production of large amounts of VEGF, which leads to hyperproliferative changes in the retinal vasculature. Furthermore, IGF-1 is hypothesized to mitigate insulin resistance. Thus, a deficiency in IGF-1 may result in fluctuating BG levels, potentially contributing to onset of ROP. It is not clear whether hyperglycemia is a clinical manifestation of low IGF-1 levels or the cause of ROP.

Contrary to the findings of Mohsen *et al* (41) and Vannadil *et al* (42), Nicolaeva *et al* (47) found no significant difference in mean BG levels between children with and without ROP and those with spontaneous remission of ROP, ignoring the effect of duration of hyperglycemia on ROP. A meta-analysis by Lei *et al* (48) revealed a significant association between the duration of hyperglycemia and ROP after adjusting for ORs (odds ratio, but no significant association between average glucose levels and the incidence of ROP. The aforementioned studies therefore suggest that the risk factors for ROP are associated with the duration of hyperglycemia rather than the average glucose levels.

In addition, association between glycated Hb (HbA1c) and ROP has been studied. Movsas and Muthusamy (49) showed that low HbA1c levels are associated with non-proliferative ROP (NP-ROP), while high levels of HbA1c are associated with P-ROP. This may be associated with fetal glucose exposure and metabolic conversion of HbA1c *in utero* and suggests HbA1c levels in preterm infants as a potential biomarker of ROP. Large-scale prospective studies are needed to confirm the association between levels of HbA1c and ROP.

Risk factors for ROP do not act independently. Instead, multiple factors interact and synergize. For example, it has been shown that hyperglycemia is closely linked to MPV (50). In diabetic patients, vascular endothelial disease accelerates PLT activation and increases peripheral blood MPV, which in turn accelerates the progression of retinopathy (31). The impact of neonatal hyperglycemia on ROP development is still unclear and requires further investigation.

Effect of inflammatory cells and factors on ROP

Influence of inflammatory cells on ROP. Both maternal systemic inflammation during pregnancy and neonatal inflammatory exposure increase the risk for ROP (51). In addition, maternal inflammatory response during the antenatal period and that of the preterm infant during the postnatal period are associated with the development of ROP. Prenatal inflammation is predominantly histological chorioamnionitis (HCA) and the newborn postnatal inflammation is primarily due to prematurity-related sepsis. HCA is a prevalent inflammatory condition during the perinatal period. HCA is a maternal reaction to infection of the chorionic and placental membranes of the amniotic membrane in the uterus, with bacterial infection as the primary cause of chorioamnionitis (52). The inflammatory response in both the mother and the fetus is the primary risk factor for severe ROP (51). A meta-analysis indicated that maternal chorioamnionitis increases risk of developing ROP (53).

Sepsis is a type of systemic inflammatory response syndrome (SIRS) caused by infection by pathogens (including bacteria, viruses and protozoa). A meta-analysis revealed a substantial association between sepsis and the progression of ROP (54). Early-onset neonatal sepsis exhibits a stronger connection with severe ROP compared with late-onset sepsis. In addition, the majority of cases of early-onset neonatal sepsis are associated with intrauterine infection, indicating a potential association between maternal systemic inflammation and an increased risk of ROP in their offspring (55). Early severe SIRS has been observed in C57BL/6 wild-type mice model to result in abnormal retinal vascular development and increased vascular anastomoses, which are associated with microglia activation (56). Childhood sepsis is associated with the development of ROP and is significantly associated with development of severe ROP (55). A meta-analysis by Wang *et al* (54) also drew a similar conclusion that sepsis is strongly associated with the degree of ROP at any stage, particularly severe ROP (stages III-V) and sepsis increases the risk of ROP in preterm infants. This may result from damage caused by pathogenic microorganisms and their toxins to the vascular endothelium. This increases the likelihood of leukocytes adhering to vessel walls and forming microthrombi within the small retinal vessels. These microthrombi may obstruct blood flow and cause vascular leakage. Secondly, infected infants may experience pulmonary and respiratory failure as blood pressure drops and hypoxia and changes in blood flow occur (54). In addition, post-sepsis hypotension and changes in oxygen saturation may affect retinal perfusion and worsen retinal ischemia (9). Neutrophil count is the most direct indicator of inflammation. Study has shown that preterm infants with ROP have a higher neutrophil count in their first month than non-ROP preterm infants (57).

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are potential inflammatory markers for diagnosing and prognosing medical conditions, such as acute myocardial infarction and cancer (58,59). Recent studies (10,60) have explored their association with ROP. In a study of CBC in preterm infants 1 week after birth, it was found that NLR is higher in premature infants who develop ROP compared with those who do not and that NLR is independently associated with development of ROP (10). However,

a study has not found an association between NLR and the development of ROP but hypothesize that NLR may serve as a risk factor for ROP requiring treatment (60). Contrary to these findings, Ozturk *et al* (61) found that neither NLR nor PLR are predictive risk factors for treatment in children with ROP. This may be due to the effect of selecting cases of CBC from preterm infants within 24 h of birth and the immature neonatal immune system. Systemic Immunoinflammatory Index (SII) is a relatively new indicator, initially used as a prognostic indicator for hepatocellular carcinoma; however, it is now also used in inflammatory disease (62,63). SII is calculated from lymphocyte, neutrophil and PLT counts, representing a homeostatic balance between inflammatory, immune and thrombotic states (64). SII is calculated as follows: PLT count x neutrophil count/lymphocyte count (65). Akdogan *et al* (57) first identified SII as an independent predictor of ROP development. They found that preterm infants with ROP have a significantly higher SII than preterm infants without ROP. A recent study (66) proposed that the C-reactive protein/albumin ratio (CAR) may be a marker for the development of ROP. During the first month of life, CAR is significantly higher in preterm infants with ROP than in those without ROP and CAR was also significantly higher in the treated than in the untreated group, suggesting that there may be an association between postnatal inflammation and ROP severity.

In conclusion, inflammation and infection are associated, and maternal chorioamnionitis and sepsis in preterm infants have a strong association with the development of ROP. Neutrophils, NLR, PLR, SII and CAR serve as indicators of inflammatory response in ROP, but the results of NLR in patients with ROP are controversial, which may be associated with time of collection of blood specimens from the children. There are fewer studies on the association between inflammatory factors such as NLR, PLR, SII, CAR and ROP, which needs to be confirmed by a large number of studies.

Effect of inflammatory factors on ROP. The study of inflammatory factors has improved the understanding of the pathogenesis and etiology of ROP (67-70). IL-6 is a proinflammatory cytokine that serves roles in inflammation and immune responses and is a key early indicator of inflammation. IL-8 has multiple functions, including recruiting neutrophils to inflammation sites, cell adhesion, tumor growth, angiogenesis, neuronal protection and brain development (70). Several eye diseases show high levels of IL-8 and IL-6, highlighting the importance of inflammation in these conditions, such as age-related macular degeneration and retinal vein obstruction (71,72). Hellgren *et al* (73) explored the association between inflammatory factors, insulin-like growth factor I (IGF-I) levels and ROP, demonstrating that inflammatory factors directly or indirectly influence the development of ROP. Elevated postnatal proinflammatory cytokine concentrations are associated with decreased IGF-I levels and ROP since inflammatory factors may inhibit certain components of the IGF-I pathway. Many cytokines share signaling components with IGF-I, such as extracellular signal-regulated kinase 1/2 and mitogen-activated protein kinase. Studies have found that the inflammatory factors IL-6 and IL-8 in amniotic fluid are independently associated with an increased risk of ROP development and progression (67,74). This is consistent with the results of a previous study, which suggested that elevated cord plasma IL-6 levels may be used as an independent predictor of severe ROP and laser treatment (68). Elevated IL-6 is significantly associated with increased risk of developing stage ≥II ROP, suggesting its potential as a biomarker for ROP risk prediction (69). Preterm infants with ROP who require treatment exhibit significantly higher levels of IL-8 compared with those who do not require treatment. However, AUROC (area under the receiver operating characteristic) curves are not effective at identifying serum IL-8 (67,70). The aforementioned studies suggest that the pathophysiological factors that predispose preterm infants to ROP are present prenatally. Therefore, therapeutic strategies to decrease the risk of ROP (specific treatment with antibiotics, anti-inflammatory and/or anti-angiogenic drugs) can be implemented during pregnancy. In conclusion, both prenatal and postnatal inflammatory factors contribute to etiology of ROP.

However, a study (75) did not find that cytokine levels in cord blood (IL-1b, IL-4, IL-6, IL-8, IL-10 and TNF-a) were associated with the risk of ROP, suggesting that measurement of cytokine levels in cord blood samples from preterm infants may be of little value in predicting ROP. Overall, the aforementioned studies highlight the need for monitoring inflammatory markers in preterm infants and future studies should focus on larger, multicenter cohorts and explore the mechanistic pathways between inflammation and ROP.

Effect of blood lipids on ROP. There are limited studies (11,76) on the effect of lipid metabolism disorders on ROP. Yang *et al* (11) used mass spectrometry to investigate the link between metabolic changes and the disease. They found significant metabolic disturbances in plasma of the children in the ROP group compared with the non-ROP group, including elevated lipid levels and hyperactivity of lipid metabolism. The retina is rich in lipids and lipid oxidation is a key energy source for the retina. Dyslipidemia can affect pathological angiogenesis in the retina (11). Abnormal activation of lipid metabolic pathways in ROP may lead to lactate accumulation and ketone body production. Dyslipidemia may manifest as elevated serum total cholesterol, low-density lipoprotein and triglyceride levels or decreased serum high-density lipoprotein concentrations (11).

Association between adiponectin (APN) and ROP development has also been investigated (76-78). Adipocytes produce endogenous bioactive protein lipocalin, which regulates lipid and glucose metabolism by promoting fatty acid oxidation and inhibiting lipid synthesis, thus decreasing triglyceride and cholesterol levels in blood. Studies have shown that preterm infants with ROP have lower levels of APN compared with those without ROP (76,77). Lipocalin may inhibit neovascularization by regulating serum levels of TNF-α, IGF-1, ω-3 long-chain polyunsaturated fatty acids (ω-3 LCPUFAs) and VEGF, thereby inhibiting occurrence and development of ROP. Furthermore, preterm birth results in a decreased supply of factors such as IGF-1, ω-3 LCPUFAs and APN from the maternal-placental interface to the fetus. This leads to metabolic disorders, insulin system immaturity and insulin resistance in preterm infants (79). There are few

studies (11,76,77) on the effect of lipids and lipocalin levels on ROP in children with ROP and further research is necessary to validate this.

4. Association between plasma metabolic pathways and ROP

In recent years, mass spectrometry has emerged as a prominent analytical technique in metabolomic studies (11,80) of ROP. Yang *et al* (11) identified the plasma metabolic pathways in infants with ROP. These metabolic pathways include glycolysis, redox homeostasis and the arginine pathway. The aforementioned study observed elevated levels of glycolytic intermediates in plasma of infants with ROP, which suggests that aerobic glycolysis is hyperactive in ROP. The aerobic glycolytic pathway is responsible for the production of ATP, which is essential for the migration of vascular endothelial cells. This is consistent with notable proliferation of endothelial cells involved in neovascularization in ROP. The oxidized pentose phosphate pathway (oxPPP) also serves an important role in endothelial cell activity and migration. oxPPP has increased levels of NADPH compared with other oxidative decomposition pathways, which produces large amounts of ROS, which may lead to a decrease in the production of associated metabolites (such as creatinine). The arginine pathway is associated with development of ROP, as evidenced by significantly lower plasma ornithine levels observed in children with ROP. This may be associated with decreased arginase activity. Inhibition of arginase activity may result in activation of NOS. Metabolomic profiling of ROP may provide insights for development of new therapeutic approaches, although further validation is required to ascertain its clinical significance (11).

5. Conclusion

In conclusion, the study of blood markers has enhanced understanding of the etiology of ROP, indicating that ROP is not only a retinal disease, but also associated with systemic responses. The etiology of ROP is multifaceted, with numerous contributing factors. Thus, it is key to explore a minimally invasive, effective and unbiased examination method for diagnosing and treating ROP. Hematological markers suggest potential risk factors for ROP development and further studies are necessary to clarify its exact pathogenesis.

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Authors' contributions

QM and WT conceived the study and wrote the manuscript. WT, YZ, HZ, KL, ZZ, HM, XJ, ZJ and QM critically revised the manuscript for intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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