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ORIGINAL RESEARCH

Risk Factors for Neonatal White-Centered Retinal Hemorrhages: Clinical Implications for Prevention

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Background: Neonatal white-centered retinal hemorrhage (NWCRH) is characterized by white or yellowish-white central spots within retinal hemorrhages, resembling Roth spots. Elucidating the etiological factors may enhance preventive strategies and deepen understanding of NWCRH. This study examined correlations between NWCRH and perinatal maternal conditions, delivery factors, and neonatal characteristics.

Methods: From January 2013 to December 2015, neonates delivered at the Department of Obstetrics at Zhongshan People's Hospital underwent RetCam III fundus screening within four days postpartum were enrolled. Demographic and clinical information of neonates and mothers were collected, and univariate and multivariate logistics regression analyses were used to explore the influencing factors of NWCRH and its severity.

Findings: WCRH was identified in 574 out of 3606 neonates (15.92%), with retinal hemorrhage detected in 868 cases (24.07%). For Grade I retinal hemorrhage, 441 cases were documented, with WCRH present in 169 cases (38.32%). For Grade II retinal hemorrhage, 239 cases were recorded, with 223 (93.31%) exhibiting WCRH. In Grade III retinal hemorrhage, 182 out of 188 cases (96.81%) displayed WCRH. In the multivariate analysis of Groups II and III, neonatal blood type B was found to be statistically significant for Roth spot formation. In the univariate analysis of maternal factors, gestational diabetes and hypertension were associated with an increased risk of Roth spots.

Conclusion: This study identified key risk factors for the formation of neonatal Roth spots, including mode of delivery, umbilical cord around the neck, and blood group B. Given its potential long-term effects on vision, early screening and preventive measures are recommended. For neonates with a history of umbilical cord around the neck and rapid delivery, fundus screening can facilitate timely intervention and improve neonatal eye health.

Keywords: Roth spots, neonatal white-centered retinal hemorrhage, full-term infants, Roth spot-like changes

Introduction

Neonatal White-Centered Retinal Hemorrhage (NWCRH) refers to the appearance of a white or yellowish-white spot centrally located within a retinal hemorrhage in neonates, resembling Roth spot-like formations. Roth spots, or hemorrhagic retinal lesions, are a distinctive type of retinal hemorrhage characterized by retinal edema and yellow-white exudates. Since Roth spots were initially identified, researchers have increasingly observed them across a variety of diseases, extending beyond infectious endocarditis. These spots have been documented in infectious diseases such as subacute bacterial endocarditis, ocular toxoplasmosis, rickettsial infections, malaria, and AIDS;[1–4] hematologic conditions like pernicious anemia and leukemia;[5,6] ocular pathologies including diabetic retinopathy, hypertensive retinopathy, endophthalmitis, and post-glaucoma surgery complications;[1,7,8] as well as in other contexts like shaken baby syndrome, acute reduction in ocular pressure, hypoxic events, trauma, and traumatic delivery in neonates.[1] Most case reports of Roth spots in these conditions are isolated and not universally documented. Some studies have indicated that optic nerve flame hemorrhages (48%) and white-centered retinal hemorrhages (30%) are the most common forms of neonatal fundus

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hemorrhage,[9] suggesting a relatively high incidence. Despite this prevalence, these conditions have seldom been the focus of extensive scholarly investigation.

At present, the etiology of NWCRH is not clear. Previous studies have mostly focused on the overall incidence and type of NWCRH, but there are few studies on the specific type of white heart retinal hemorrhage, resulting in insufficient understanding of its clinical risk factors. In addition, the screening and diagnosis of NWCRH also faces many challenges, such as poor neonatal cooperation, high screening equipment and technical requirements, which further limit the development of related studies.

This study aims to fill this knowledge gap by analyzing the risk factors associated with white retinal hemorrhage in full-term neonates, and exploring its relationship with maternal, childbirth, and neonatal factors, in order to provide a basis for clinical prevention and intervention, and to deepen the understanding of the similarities and differences between neonatal and adult Roth spots. The results of this study will help to improve the early recognition and management of NWCRH and improve the visual health prognosis of neonates.

Methodology

Study Population

All study subjects were neonates born at the Department of Obstetrics, Zhongshan University Affiliated Zhongshan Hospital (Zhongshan People's Hospital), from January 2013 to December 2015, totaling 3606 infants. With parental consent, each infant underwent fundus screening.

Inclusion criteria consisted of full-term neonates with a gestational age of 37 weeks or more and an Apgar score greater than 9. Exclusion criteria involved the presence of ocular diseases, such as familial exudative vitreoretinopathy, congenital cataract, and primary congenital glaucoma. Ethical approval for this study was obtained from the Ethics Committee of Zhongshan University Affiliated Zhongshan Hospital (Zhongshan Aierlun Review Document No. (2020) KYPJ001). All the methods were carried out in accordance with the Declaration of Helsinki. This consent covered not only the fundus screening but also participation in the research study as a whole.

Data Collection

Detailed medical history and relevant maternal, delivery, and neonatal factors were documented for each neonate. Maternal factors included age, history of cesarean section, vaginitis, intrauterine infection, gestational diabetes, gestational hypertension, anemia, thalassemia, placental abruption, premature rupture of membranes, preeclampsia, and eclampsia. Delivery factors encompassed delivery method [spontaneous vaginal delivery (SVD) or cesarean section (CS)], birth canal lacerations (including cervical, vaginal, and perineal lacerations), postpartum hemorrhage, durations of the first and second stages of labor, fetal biparietal diameter, and amniotic fluid index (assessed by ultrasound within one week before birth). Neonatal factors recorded included sex, blood type, gestational age, birth weight, presence of nuchal cord, cephalohematoma, intracranial hemorrhage, neonatal glucose-6-phosphate deficiency, fetal aspiration syndrome, congenital heart disease, neonatal hyperbilirubinemia, and maternal-infant ABO blood type incompatibility.

Eye Examination

Eye examinations were conducted within four days of birth, with an average examination timing of (1.81 ± 1.30) days post-birth. All examinations, imaging, and image analyses were carried out by a team consisting of experienced ophthalmologists and nurses specializing in fundus examination. Initial assessments of the anterior segment and pupillary light reflex were conducted with a standard flashlight. Pupil dilation was achieved using 1% compound tropicamide eye drops (Santen Pharmaceutical Co., Japan), administered every 10 minutes for a total of three applications, along with topical anesthesia (Alcaine eye drops, Alcon). An eyelid speculum was employed to maintain eye openness, and digital images were captured using a RetCam III (Clarity Medical Systems, California, USA) equipped with a 130° wide-angle lens. Two experienced reviewers (Yanli Zhang and Yu Lin) independently interpreted the images, with any disagreements resolved by a third senior reviewer. In addition, all three doctors received training and passed the assessment before the study began.

Figure 1 displays images of neonatal white-centered retinal hemorrhages.

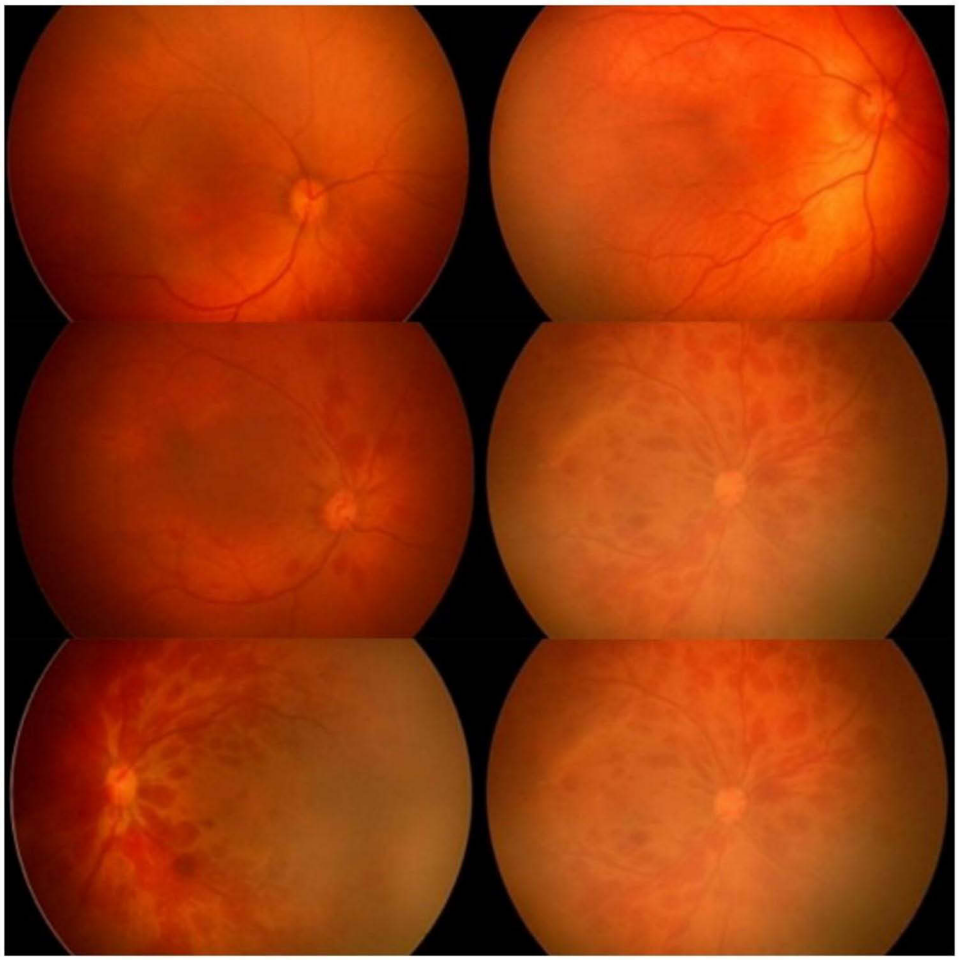

Figure 1 Digital Images of Neonatal White-Centered Retinal Hemorrhage.

Screening for NWCRH

Retinal hemorrhages were classified according to the Egge classification into three grades: Grade I, defined as small retinal hemorrhages localized around the optic nerve, presenting as dot or fine linear bleeding; Grade II, with a slightly larger extent of retinal hemorrhage than Grade I, characterized by patchy, dot, blot, or flame-shaped hemorrhages not exceeding the diameter of the optic disc; and Grade III, involving retinal hemorrhages extending beyond the optic disc diameter, displaying a line of flame-shaped hemorrhage along vessels, and/or macular hemorrhage (macular hemorrhage alone qualifies as Grade III), as detailed in Table 1. If the hemorrhage severity differed between the two eyes, the classification was based on the eye with the more severe hemorrhage.

NWCRH refers to a white spot or yellow-white exudative lesion at the center of a retinal hemorrhage in neonates. Based on screening results, neonates without retinal hemorrhage or white-centered retinal hemorrhage were designated as the control group, while those with neonatal white-centered retinal hemorrhage were assigned to the positive group. The presence of a central white spot or yellow-white exudative lesion within the retinal hemorrhage qualifies a case as positive, irrespective of whether it is observed in one or both eyes. Not all cases of neonatal retinal hemorrhage exhibit Roth spot-like changes in the fundus.

To further investigate the risk factors associated with neonatal white-centered retinal hemorrhage, a subgroup analysis was conducted. For Grade I hemorrhage, neonates without Roth spot-like changes served as the control group, while those exhibiting Roth spot-like changes were classified as the positive group. This subgrouping approach was subsequently applied to Grade II and Grade III hemorrhages for a more detailed analysis. The grouping method used is illustrated in Figure 2.

Table 1 Retinal Haemorrhages Were Graded According to Egge's Classification

Grade	Description
Grade 1	Small retinal haemorrhage confined to the area around the optic nerve, associated with dot or fine linear bleeding.
Grade 2	Slightly larger amount of retinal haemorrhage than Grade 1; patchy, dot, blot or flame-shaped haemorrhage, size does not exceed the optic disc diameter.
Grade 3	Retinal haemorrhage more than the diameter of the optic disc area, a line of flame-shaped haemorrhage along vessels, macular haemorrhage (alone constitutes Grade 3).

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 software. Univariate logistic regression was applied to compare maternal, delivery, and neonatal factors between the group exhibiting Roth spot-like changes and the group without retinal hemorrhage or Roth spot-like changes. Factors with a P-value of < 0.1 in the univariate analysis were further analyzed using multivariate logistic regression. In the multivariate analysis, a P-value < 0.05 was considered statistically significant. Similarly, comparisons were made between the Grade I retinal hemorrhage group with Roth spot-like changes and the Grade I group without such changes, as well as between Grade II and Grade III groups with and without Roth spot-like changes.

Results

Univariable Analysis

In Group 1, univariate analysis identified statistically significant maternal factors, including a history of cesarean section (OR = 0.18, 95% CI 0.12–0.27, P < 0.1), gestational diabetes (OR = 0.64, 95% CI 0.43–0.97, P = 0.026), and gestational hypertension (OR = 0.59, 95% CI 0.34–1.04, P = 0.052). Significant delivery factors included delivery mode (OR = 0.08, 95% CI 0.05–0.11, P < 0.1) and birth canal lacerations (OR = 3.15, 95% CI 2.61–3.81, P < 0.1). For neonatal factors, gender (OR = 1.23, 95% CI 1.03–1.48, P = 0.023) and nuchal cord (OR = 1.59, 95% CI 1.31–1.92, P < 0.1) were statistically significant, while congenital heart disease, fetal aspiration syndrome, and glucose-6-phosphate dehydrogenase deficiency showed no significant associations.

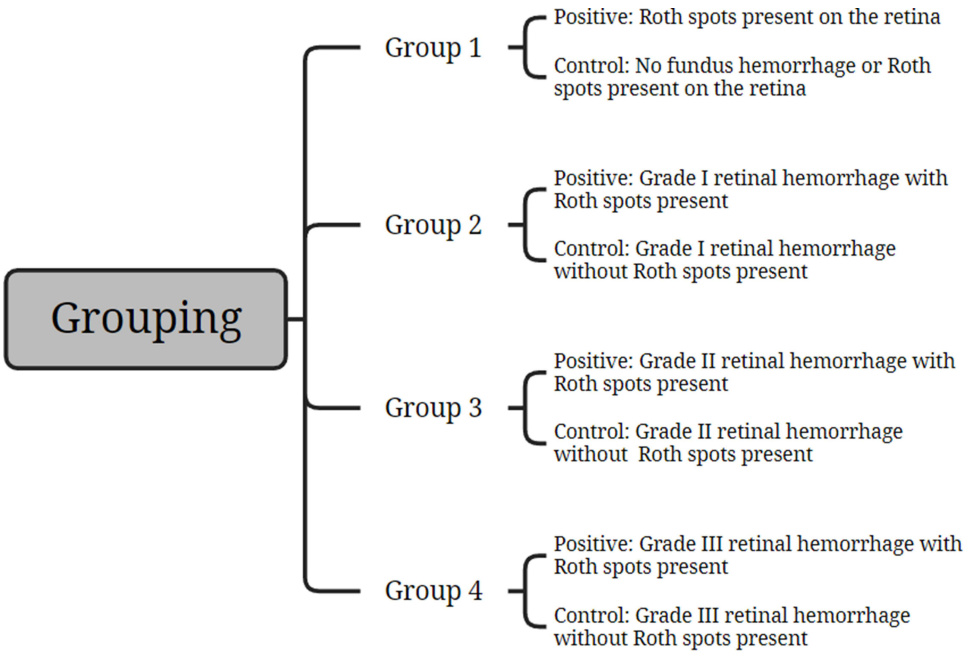

Figure 2 Grouping Method.

In Group 2, significant maternal factors included birth canal lacerations, premature rupture of membranes, and thalassemia. Among delivery factors, the duration of the second stage of labor was significant, and among neonatal factors, blood type, neonatal G6PD deficiency, and nuchal cord were identified as significant. In Group 3, significant factors included a maternal history of cesarean section and pregnancy-induced hypertension, delivery mode, and neonatal factors of blood type and congenital heart disease. In Group 4, significant factors included delivery mode among maternal factors, as well as blood type and nuchal cord among neonatal factors. Detailed results are presented in Table 2.

Table 2 Univariate and Multivariate Logistic Regression Analysis of Factors Associated with Neonatal White-Centered Retinal Hemorrhage

Factors	Group		Univariate Analysis		Multivariate Analysis	
	No Roth Spots (n=2738)	Roth Spots (n=574)	HR (95% CI)	p*	HR (95% CI)	p
Maternal Factors						
Maternal Age						
History of Cesarean Section	518 (18.92)	23 (4.01)	0.18 (0.12, 0.27)	0.000	1.19 (0.69, 2.02)	0.534
Anemia	106 (3.87)	20 (3.48)	0.90 (0.55, 1.46)	0.656		
Vaginitis	71 (2.59)	17 (2.92)	1.15 (0.67, 1.96)	0.623		
Intrauterine Infection	2 (0.07)	0 (0.00)	0.50 (0.12, 2.15)	0.308		
Thalassemia	88 (3.21)	25 (4.36)	1.37 (0.87, 2.16)	0.185		
Gestational Diabetes	202 (7.38)	28 (4.88)	0.64 (0.43, 0.97)	0.026	0.72 (0.47, 1.11)	0.135
Premature Rupture of Membranes	479 (17.49)	87 (15.16)	0.84 (0.66, 1.08)	0.171		
Placental Abruption	6 (0.22)	1 (0.17)	0.79 (0.10, 6.61)	0.827		
Gestational Hypertension	111 (4.05)	14 (2.44)	0.59 (0.34, 1.04)	**0.052**	0.92 (0.50, 1.67)	0.776
Preeclampsia	62 (2.26)	10 (1.74)	0.77 (0.39, 1.50)	0.422		
G6PD Deficiency	23 (0.84)	8 (1.39)	1.67 (0.74, 3.75)	0.235		
Delivery Factors						
Delivery Mode (Vaginal/CS): Cesarean	1075 (39.36)	27 (4.73)	0.08 (0.05, 0.11)	0.000	0.09 (0.06, 0.15)	0.001
Assisted Delivery	19 (0.69)	2 (0.35)	0.50 (0.12, 2.15)	0.308		
Birth Canal Laceration	1064 (38.86)	383 (66.72)	3.15 (2.61, 3.81)	0.000	1.41 (1.15, 1.74)	0.001
Postpartum Hemorrhage	70 (2.56)	13 (2.26)	0.88 (0.49, 1.61)	0.680		
Duration of First Stage of Labor (hours): Prolonged	98 (6.06)	27 (4.99)	0.81 (0.53, 1.26)	0.347		
Duration of Second Stage of Labor (hours)	6 (0.37)	5 (0.92)	2.50 (0.76, 8.21)	0.144		
Biparietal Diameter (mm): Excessive	48 (1.77)	7 (1.23)	0.69 (0.31, 1.54)	0.346		
Amniotic Fluid Index (mm): Insufficient	590 (21.76)	118 (20.77)	0.94 (0.75, 1.18)	0.601		
Neonatal Factors						
Gender (Female)	47.7%	52.3%	1.23 (1.03, 1.48)	0.023	1.20 (0.99, 1.45)	0.061
Birth Weight (Normal)	2716 (99.27)	566 (98.61)	0.52 (0.23, 1.19)	0.141		
Nuchal Cord	734 (26.81)	211 (36.76)	1.59 (1.31, 1.92)	0.000	1.41 (1.16, 1.72)	0.001
Cephalohematoma	3 (0.11)	2 (0.35)	3.19 (0.53, 19.12)	0.233		
Intracranial Hemorrhage	4 (0.15)	1 (0.17)	1.19 (0.13, 10.68)	0.877		
Neonatal Hyperbilirubinemia	734 (26.81)	172 (29.97)	1.17 (0.96, 1.42)	0.126		
Maternal-Fetal ABO Blood Incompatibility	30 (1.10)	7 (1.22)	1.11 (0.49, 2.55)	0.800		
Neonatal Blood Type A	660 (25.19)	131 (23.60)		0.684		
Neonatal Blood Type B	198 (7.56)	37 (6.67)	1.08 (0.84, 1.40)			
Neonatal Blood Type AB	749 (28.59)	161 (29.01)	0.94 (0.63, 1.40)			
Neonatal Blood Type O	1013 (38.66)	226 (40.72)	1.12 (0.89, 1.42)			
Fetal Aspiration Syndrome	13 (0.47)	1 (0.17)	0.37 (0.05, 2.80)	0.263		
Congenital Heart Disease	13 (0.47)	2 (0.35)	0.73 (0.16, 3.26)	0.672		
G6PD Deficiency	12 (0.44)	5 (0.87)	2.00 (0.70, 5.69)	0.220		

Note: *bolded p value < 0.1.

Multivariate Analysis

Factors identified as significant in the univariate logistic regression analysis were further examined using multivariate logistic regression. Results revealed that, in Group 1, neonatal white-centered retinal hemorrhage was significantly associated with delivery mode (OR = 0.09, 95% CI 0.06–0.15, P < 0.001), birth canal lacerations (OR = 1.41, 95% CI 1.15–1.74, P = 0.001), and nuchal cord (OR = 1.41, 95% CI 1.16–1.72, P < 0.001). In Group 2, blood type B (OR = 2.14, 95% CI 1.19–3.85, P = 0.011) and birth canal lacerations (OR = 2.21, 95% CI 1.38–3.55, P < 0.001) showed significant associations. In Group 3, blood type B was significantly associated with an increased likelihood of Roth spots (OR = 10.79, 95% CI 1.10–105.45, P = 0.041). In Group 4, no statistically significant associations were identified among the influencing factors. Details are provided in Table 2.

Multivariate Analysis Results: Grade I Retinal Hemorrhage with Roth Spots versus Without Roth Spots

The multivariate analysis comparing Grade I retinal hemorrhage cases with and without Roth spots revealed significant associations with blood type B (OR = 2.14, 95% CI 1.19–3.85, P = 0.011) and birth canal lacerations (OR = 2.21, 95% CI 1.38–3.55, P = 0.001). No other factors demonstrated statistical significance, as shown in Table 3.

Multivariate Analysis Results: Grade II Retinal Hemorrhage with Roth Spots versus Without Roth Spots

For Grade II retinal hemorrhage, blood type B was significantly associated with Roth spot presence, with an odds ratio of 10.79 (95% CI 1.10–105.45, P = 0.041), indicating a higher likelihood of Roth spots in neonates with blood type B. No other factors exhibited a statistically significant association, as presented in Table 4.

Multivariate Analysis Results: Grade III Retinal Hemorrhage with Roth Spots versus Without Roth Spots

In Grade III retinal hemorrhage cases, none of the evaluated factors, including blood types AB, B, and O, delivery mode (vaginal delivery versus cesarean section), or nuchal cord, were statistically associated with Roth spot presence. All factors yielded P-values > 0.05, indicating no significant correlation with Roth spots in this group, as outlined in Table 5.

Table 3 Multivariate Analysis of Factors Associated with Roth Spots in Grade I Retinal Hemorrhage

Factors	HR (95% CI)	p
Blood Type (A=1, B=2, AB=3, O=4): 3	1.78 (0.68, 4.66)	0.239
Blood Type (A=1, B=2, AB=3, O=4): 2	2.14 (1.19, 3.85)	0.011
Blood Type (A=1, B=2, AB=3, O=4): 4	1.25 (0.72, 2.18)	0.426
Neonatal G6PD Deficiency (Yes=1, No=0): 1	0.00 (0.00, Inf)	0.984
Thalassemia (Yes=1, No=0): 1	0.19 (0.02, 1.58)	0.124
Birth Canal Laceration (Yes=1, No=0): 1	2.21 (1.38, 3.55)	0.001
Premature Rupture of Membranes (Yes=1, No=0): 1	0.83 (0.46, 1.48)	0.52
Nuchal Cord (Yes=1, No=0): 1	1.55 (0.99, 2.42)	0.054
Second Stage of Labor Duration (hours): Prolonged (Yes=1, No=0): 1	0.00 (0.00, Inf)	0.985

Table 4 Multivariate Analysis of Factors Associated with Roth Spots in Grade II Retinal Hemorrhage

Factors	Multivariate Analysis	
	HR (95% CI)	p
Blood Type (A=1, B=2, AB=3, O=4): 3	0.99 (0.20, 4.91)	0.995
Blood Type (A=1, B=2, AB=3, O=4): 2	10.79 (1.10, 105.45)	0.041
Blood Type (A=1, B=2, AB=3, O=4): 4	2.50 (0.69, 9.10)	0.165
Mode of Delivery (Vaginal=1, Cesarean=2): 2	0.38 (0.02, 6.35)	0.503
Congenital Heart Disease (Yes=1, No=0): 1	0.00 (0.00, Inf)	0.991
History of Cesarean Section (Yes=1, No=0): 1	0.79 (0.05, 12.21)	0.869
Gestational Hypertension (Yes=1, No=0): 1	0.04 (0.00, 1.29)	0.069

Table 5 Multivariate Analysis of Factors Associated with Roth Spots in Grade III Retinal Hemorrhage

Factors	Multivariate Analysis	
	HR (95% CI)	p
Blood Type (A=1, B=2, AB=3, O=4): 3	0.00 (0.00, Inf)	0.996
Blood Type (A=1, B=2, AB=3, O=4): 2	0.00 (0.00, Inf)	0.996
Blood Type (A=1, B=2, AB=3, O=4): 4	0.00 (0.00, Inf)	0.997
Mode of Delivery (Vaginal=1, Cesarean=2): 2	0.23 (0.03, 1.66)	0.144
Nuchal Cord (Yes=1, No=0): 1	81350585.62 (0.00, Inf)	0.996

Discussion

With the growing demand for eye health, researchers are increasingly focusing on fundus diseases; however, studies on neonatal fundus diseases remain limited due to challenges with neonatal cooperation during eye screenings. Recently, neonatal retinal hemorrhage has garnered more attention, though studies specifically on neonatal white-centered retinal hemorrhage (WCRH), resembling Roth spot changes, remain sparse. Roth spots are commonly observed in adult retinal hemorrhages, primarily documented in case reports, suggesting a low occurrence in adults. In our study, WCRH was identified in 574 out of 3606 neonates (15.92%), with retinal hemorrhage detected in 868 cases (24.07%). International literature reports that the most prevalent forms of neonatal retinal hemorrhage are optic nerve flame hemorrhages (48%) and white-centered retinal hemorrhages (30%).[10] Our study also observed that Roth spot-like changes are relatively common in neonatal retinal hemorrhages. Specifically, among neonates with Grade I retinal hemorrhage, 441 cases were documented, with WCRH present in 169 cases (38.32%). For Grade II retinal hemorrhage, 239 cases were recorded, with 223 (93.31%) exhibiting WCRH. In Grade III retinal hemorrhage, 182 out of 188 cases (96.81%) displayed WCRH, indicating a positive correlation between hemorrhage severity and WCRH occurrence. The underlying mechanism of WCRH formation may account for this correlation. Some researchers suggest that the white-centered spots may be septic emboli,[11] while others propose that WCRH formation is often linked to microvascular changes within the retina, such as microvascular rupture, vascular leakage, and thrombosis. These processes may involve platelet adhesion and aggregation, leading to fibrin formation as part of capillary repair. Alternatively, the accumulation of blood cells or exudates within retinal tissue could form the characteristic bright white spots.[1]

Literature reports that retinal white-centered hemorrhages are commonly observed in systemic diseases associated with low platelet counts, such as leukemia and systemic lupus erythematosus.[6] In neonates, platelets exhibit low reactivity within the first few days after birth due to immature platelet function. However, this reduced platelet reactivity and lowered levels of coagulation factors are often balanced by other hemostatic factors in neonates, including elevated von Willebrand factor, hematocrit, mean corpuscular volume (MCV), and reduced natural anticoagulants.[12,13] These compensatory mechanisms enable neonates to maintain a primitive physiological hemostatic system, though the response of this fragile system to pathological challenges remains unclear. Platelets play a crucial role in vascular integrity maintenance. Under pathological conditions, damage to capillary endothelial cells, coupled with altered platelet adhesion and coagulation cascades—along with neonatal platelet hypo-reactivity—may lead to coagulation factor depletion, increased bleeding risk, and capillary disruption. This ultimately results in the leakage of vascular components and cells, leaving platelet-fibrin thrombi formed as part of the platelet repair process following endothelial damage.

The presence of a nuchal cord has been identified as a risk factor for Roth spot formation, as it can impact the delivery process and is associated with an increased likelihood of oxytocin-augmented labor. Such cases often experience a prolonged second stage of labor,[14] particularly when the nuchal cord is tightly wrapped or looped multiple times around the fetal neck, raising the risk of fetal hypoxia.[15] Additionally, nuchal cord compression restricts fetal blood flow, limiting the supply of oxygen and nutrients, which can lead to fetal ischemia (reduced blood flow) and asphyxia (oxygen deficiency).

Retinal capillaries are especially susceptible to hypoxia, which compromises their stability through mechanisms involving polyamines, KATP channels, calcium influx, and calcium-dependent pathways.[16] Hypoxia-induced metabolic

acidosis can lead to lysosomal rupture within cells, triggering autolysis and necrosis of retinal capillary endothelial cells. Furthermore, intracellular oxidative stress and excessive production of oxygen free radicals result in oxidative damage to retinal vascular walls. Hypoxia may also cause retinal vascular spasms, an adaptive response to oxygen deficiency that prioritizes blood flow to vital organs. However, prolonged vascular spasms can slow blood flow and further reduce oxygen supply to the retina.

Hypoxia can also provoke an inflammatory response, resulting in the accumulation of leukocytes and inflammatory cells in the retinal area, further compromising vessels and surrounding tissues.[17] The subsequent leakage of leukocytes and cellular debris contributes to the formation of the characteristic bright white spots associated with Roth spots. In this study, the mode of delivery was found to influence the occurrence of Roth spot-like changes. A possible mechanism is that the process of vaginal delivery can cause mechanical injury to the eyes and retinal vasculature. Compression of the fetal head may reduce blood flow to the head, resulting in hypoxia. Pressure fluctuations can elevate retinal venous pressure, which may exacerbate retinal capillary rupture.[18]

Moreover, vaginal delivery often involves oxytocin administration to enhance uterine contractions, which in turn can increase prostaglandin levels. Elevated prostaglandin levels may disrupt the fetal blood-retinal barrier, increasing the risk of hemorrhage. Additionally, fetal retinal vasculature is underdeveloped compared to adults, with shorter vessel length, uneven vessel diameters, numerous branch points, and thinner capillary walls. Under pathological conditions, such as hypoxia and trauma, these anatomical features predispose neonates to retinal hemorrhage. Severe microvascular rupture can lead to the leakage of cells and exudates, resulting in the formation of white-centered spots within the hemorrhage. The study also identified an association between birth canal lacerations and Roth spot formation. Vaginal delivery often results in varying degrees of birth canal injury, including cervical, vaginal, and perineal tears. Strong uterine contractions or rapid labor progression may increase the risk of cervical tears, while prolonged pressure exerted on the fetus during contractions and delivery may impact blood flow to the fetal eyes, leading to hypoxia. Sudden changes in pressure can also contribute to retinal microvascular rupture. In combination with neonatal factors, such as low coagulation factor levels and reduced platelet reactivity, these conditions facilitate the formation of Roth spots. NWCRH can cause permanent changes in the structure of the retina, which can affect vision development and visual function. Long-term follow-up studies can evaluate the long-term effects of NWCRH on neonatal vision, refractive status, and retinal function, as well as the presence of potential complications such as retinal detachment, macular degeneration, etc.

In the multivariate analysis of Groups II and III, neonatal blood type B was found to be statistically significant for Roth spot formation. In the univariate analysis of maternal factors, gestational diabetes and hypertension were associated with an increased risk of Roth spots. These conditions are common complications during pregnancy. Gestational hypertension can induce systemic small artery spasms, increasing resistance in the spiral arteries of the placenta and resulting in abnormal arterial transformation and restricted uteroplacental blood flow. This restriction leads to substantial narrowing of the placental villous capillaries, calcium infarctions, and deposits, causing villous necrosis or widespread infarction and altering systemic microcirculation. Increased secretion of antidiuretic hormones further narrows vessel lumens, leading to vascular spasms, endothelial swelling, and reduced nutrient and oxygen supply to the fetus's retinal vessels.[19] In preeclampsia, fetal growth restriction may result in impaired megakaryocyte formation, increasing the risk of neonatal thrombocytopenia,[20] which weakens the endothelial lining and leaves platelet-fibrin deposits on the retina. Gestational diabetes can cause thrombosis in fetal placental vessels and the formation of nucleated red blood cells, resulting in immature, edematous, ischemic, or infarcted villi. This immature state and reduced oxygen-carrying capacity of nucleated red blood cells contribute to chronic fetal hypoxia.[21] Prolonged hypoxia can activate hypoxia-inducible factor (HIF), promoting the expression of various proangiogenic genes, including VEGF.[22] Due to the immaturity of neonatal capillary function, these vessels are more susceptible to rupture or leakage, leading to retinal hemorrhage and the deposition of white exudative material.

However, in the multivariate analysis, these factors did not retain significance, possibly due to the confounding influence of delivery factors. Mothers with these complications often face a higher risk of intrauterine hypoxia, leading to a preference for cesarean delivery to minimize risks. Given the relatively high incidence of neonatal Roth spots, their long-term impact on visual acuity and refraction remains unclear. Clinically, it is essential to implement preventive measures to address potential developmental complications. Prenatal evaluations should assess maternal birth canal

conditions, and when severe nuchal cord is detected, careful selection of the delivery method is advised to optimize outcomes for both mother and fetus.

In order to reduce the potential risk of NWCRH to the visual health of newborns, a variety of strategies are needed. First, during the prenatal and intrapartum phases, maternal and fetal monitoring should be strengthened, and high-risk factors that may lead to NWCRH should be identified and addressed in a timely manner, such as cervical spinal cord, vaginal delivery, or rapid delivery, and neonates with a history of rapid delivery should undergo fundus screening to monitor ocular development, dynamic absorption of hemorrhagic spots, and Roth spots, and timely intervention if necessary. Second, for neonates with high-risk factors, regular fundus screening and follow-up is recommended to monitor the absorption of hemorrhagic spots and the development of the retina. In addition, for neonates presenting with NWCRH, an individualized intervention plan should be developed on a case-by-case basis, such as laser therapy, medical therapy, or surgical intervention if necessary, to promote retinal repair and functional recovery.

However, there are some potential limitations to the study. First, there may be unmeasured confounding factors, such as platelet function in newborns or systemic maternal disease, that may influence the development of NWCRH. Although some known confounders were controlled for in the studies, there were other unknown or unmeasured factors that could have had an impact on the results. Second, in this study, the small sample size may have limited statistical power for stratified analyses of grade II and III retinal hemorrhages. Stratified analyses typically require large sample sizes to detect significant differences between subgroups. Due to the relatively small number of neonates with grade II and III hemorrhage, this may lead to insufficient statistical power, increasing the risk of false-negative results that fail to detect a significant association that actually exists. In addition, the smaller sample size may also result in a wide confidence interval for the results, reducing the precision and reliability of the results. Therefore, caution needs to be exercised when interpreting the results of these stratified analyses and recognizing that they may be affected by sample size limitations. Future studies could adopt a prospective cohort study design to further explore the causal relationship between these factors and NWCRH. In addition, the research mainly focuses on maternal, childbirth and neonatal factors, and there is little discussion on other environmental and socioeconomic factors that may affect NWCRH.

Conclusion

The findings underscore the importance of assessing prenatal and perinatal risk factors to reduce the risk of NWCRH. Vaginal delivery, umbilical cord around the neck, birth canal tear, and neonatal blood group B were significant risk factors for NWCRH. Given its potential long-term effects on vision, careful evaluation of high-risk factors in the prenatal and perinatal periods, as well as early fundus screening in neonates with high-risk factors, is recommended for timely detection and management of NWCRH, thereby improving the visual health prognosis of newborns. Management strategies to further reduce the incidence of NWCRH and improve the visual health of newborns are the focus of future research.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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