Systematic Review

THROMBOCYTOPENIA AS A CLINICAL BIOMARKER OF RETINOPATHY OF PREMATURITY

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ABSTRACT

Retinopathy of prematurity (ROP) is the primary cause of childhood blindness. It arises from the underdevelopment of retinal blood vessels in premature infants. Platelets have a vital function in the regulation of angiogenesis. Thus, thrombocytopenia may contribute to the progression of ROP. The objective of this systematic study was to examine the relationship between thrombocytopenia and ROP. The PubMed and Cochrane Library databases were accessed to search for retrospective, case-control, and cross-sectional studies. This study adhered to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The literature search resulted in nine records to be analyzed in our review. All the selected studies were conducted between 2017 and 2022. Seven studies reported that the prevalence of thrombocytopenia in infants with ROP ranged from 18.37% to 71%. The frequency of thrombocytopenia in preterm children without ROP was between 5.71% and 21%. Thrombocytopenia was identified as a risk factor for ROP in seven studies, with the odds ratio (OR) for thrombocytopenia ranging from 2.8 to 6.69. Thrombocytopenia in premature infants can potentially serve as a clinical biomarker in the screening of type 1 ROP. This finding suggests that thrombocytopenia may contribute to the pathophysiology of ROP. Further research is necessary to determine the critical threshold platelet count for thrombocytopenia in infants with ROP.

Keywords: Thrombocytopenia; retinopathy of prematurity (ROP); preterm infant; angiogenesis; childbirth complications

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Highlights:
1. This is the first systematic review investigating thrombocytopenia and its association with retinopathy of prematurity.
2. Thrombocytopenia can be a useful clinical biomarker in retinopathy of prematurity screening, considering the quick, affordable, and widespread availability of the examination.

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative condition that affects the vasculature of the retina in premature newborns. It has become the predominant cause of visual impairment in children globally (Kim et al. 2018). Around the world, ROP has caused at least 50,000 children to go blind. The blindness brought on by ROP occurs infrequently in developed countries. However, the occurrence of ROP leading to blindness is more common in developing countries due to a higher survival rate among premature infants, inadequate regulation of the neonatal intensive care unit (NICU), and scarce funduscopic examinations. These factors limit the frequency and accessibility of monitoring observable changes in the retinal vasculature (Wood et al. 2021).

Low gestational age and low birth weight are the primary factors that increase the risk of ROP development. According to a study by Hong et al. (2022), underdeveloped retinal vasculature and neurons are correlated with both low gestational age and birth weight due to the delicate retinal structure during birth. However, the study did not find a statistically significant relationship between birth weight and severe ROP. This finding might point to the significance of weight increase in slowing the course of ROP. Other risk factors include gender, the

need for oxygen therapy and blood transfusions, as well as the presence of patent ductus arteriosus (PDA), intraventricular extension of hemorrhage, necrotizing enterocolitis (NEC), sepsis, and newborn infections.

Elevated levels of oxygen pressure in ROP inhibit the formation of new blood vessels. As a result, the function of existing retinal capillaries will be impeded, causing non-vascularized regions within the retina. When the retina experiences hypoxia due to incomplete vascularization, it stimulates the secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF) and erythropoietin. These factors contribute to the development of neovascularization, intraocular fibrosis, and retinal detachment. VEGF and vascular permeability in the eye have a significant role in pathological neovascularization. Anti-VEGF medication has been utilized to treat ROP due to the well-established link between vascular endothelial growth factor and ROP development (Eldweik & Mantagos 2016, Wu & Wu 2017).

Thrombocytopenia can be quickly and efficiently identified using standard blood tests. Additionally, the platelet transfusion procedure is a commonly used treatment (Sola-Visner & Bercovitz 2016). During the development of ROP, understanding the etiology of thrombocytopenia in ROP may be beneficial for the screening and treatment of the disease. A recent study found a correlation between thrombocytopenia and a worse prognosis for preterm newborns with neonatal sepsis and NEC (Resch et al. 2018). This systematic review aimed to analyze the relationship between thrombocytopenia and ROP.

MATERIALS AND METHODS

Previous research conducted by Page et al. (2021) provided a reference for the literature search strategy in this study. This systematic review was carried out by adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Cochrane Library and PubMed databases were used in the comprehensive literature search in this systematic review. The search was performed to gather scholarly records of research conducted between September 2012 and September 2022. The following keywords and Boolean operators were used to search for the literature: (“Thrombocytopenia” OR “Low Thrombocyte” OR “Thrombocyte” OR “Platelet”), AND (“ROP” OR “Retinopathy of Prematurity").

We included all pertinent retrospective, case-control, and cross-sectional studies on thrombocytopenia in premature infants with ROP. Case reports, letters, editorials, review articles, inaccessible full texts, and studies in languages other than English were excluded from consideration (Pollock & Berge 2018). The flow diagram that summarizes the study selection process is exhibited in Figure 1.

Data were extracted from all of the selected studies. The general information (e.g., author and year of publication), participants, average gestational age, average birthweight, platelet count threshold for thrombocytopenia, prevalence of thrombocytopenia in infants with ROP, and the relationship between thrombocytopenia and ROP were among the collected data (Lee et al. 2017).

A checklist from the Joanna Briggs Institute was used to assess the quality and bias risk of the studies. Each item on the checklist was counted for one point. If a study received at least half of the maximum possible points, it was considered to be of high quality. If it scored fewer than half of the maximum possible points, it was deemed low quality (Lockwood & Oh 2017). Two reviewers independently assessed the quality of the studies to prevent bias. Any disagreement between the two reviewers was settled by consensus.

RESULTS

In our initial search, we discovered 117 scholarly records. Out of the 117 records, only nine original research papers were eligible for inclusion in this study. Figure 1 displays the flow diagram that demonstrates the process of the study selection. All of the studies met the high-quality standards set by the Joanna Briggs Institute. All of the selected studies included retrospective, cross-sectional, and case-control investigations. The sample sizes ranged from 9 to 240 individuals. Among the samples were infants born with multiple gestations, type 1 ROP, aggressive posterior retinopathy of prematurity (APROP), very low birth weight (VLBW), and prematurity. The mean birthweight of the newborns diagnosed with ROP varied between 585 and 1,955 grams. The infants diagnosed with ROP had a mean gestational age between 24 and 33.25 weeks. The summaries of the studies are presented in Table 1.

The platelet count threshold for thrombocytopenia exhibited variability across different studies. Among the nine studies examined in this systematic review, three used a threshold of 150,000/mL. Two studies specified a threshold of 100,000/mL. However, the remaining four studies did not specify the threshold for low thrombocyte levels.

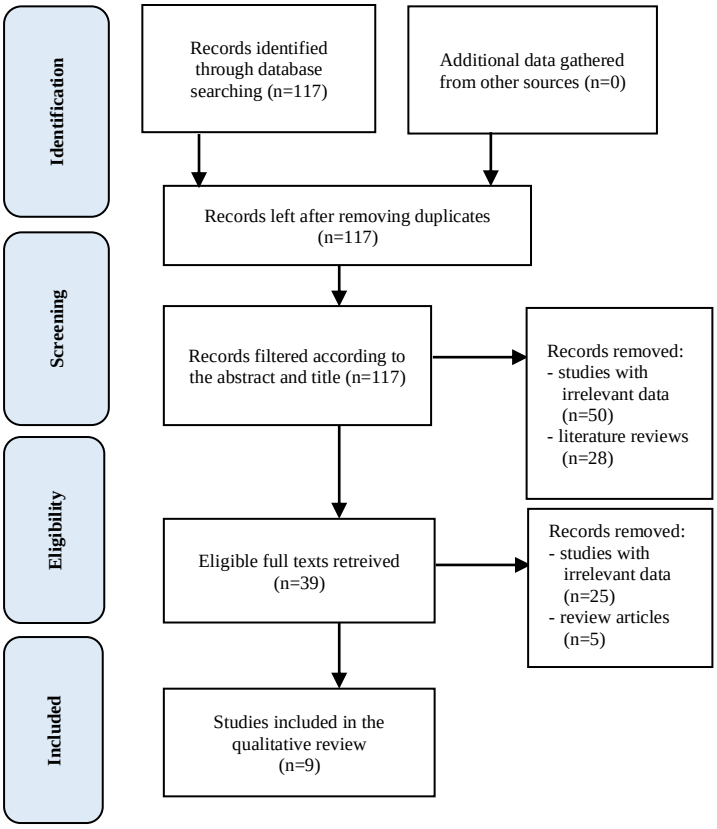

Figure 1. Flow diagram for the study selection process.

Table 1. Summaries of the characteristics of the included studies.

No	References	Research design	Total samples	Mean gestational age (weeks)	Mean birth weight (g)	Low thrombocyte level threshold	Thrombocytopenia prevalence (%)		Relationship between ROP and low thrombocyte levels
							Cases	Controls	
1	Sancak et al. (2019)	Case-control	81 infants with type 1 ROP and 81 premature infants without ROP	27.6±2.1	993±292	<150,000	71	21	RR=6.69; p<0.001
2	Cakir et al. (2018)	Retrospective	202 infants with VLBW	25.3±1	782±167	<100,000			OR=4.17; p<0.001 OR=2.97; p=0.006
3	Jensen et al. (2018)	Case-control	100 infants with type 1 ROP and 100 premature infants without ROP			<150,000			Weeks 24-28: OR=4.7; p=0.001 Weeks 29-34: OR=2.8; p=0.006 Weeks 35-38: OR=2.0; p=0.10 (not

									significant)
4	Lundgren et al. (2017)	Retrospective	9 infants with APROP and 9 infants with stadium II ROP	24±1	585 (470-700)	<100,000	56	27	Significantly lower thrombocyte counts (p<0.001) and a shorter time interval (in days) for platelet transfusion (p<0.001) among infants with APROP
5	Parrozzani et al. (2021)	Retrospective	206 infants with ROP and 357 premature infants without ROP	28.72±2.58	1083.8±329.62	-	18.37	5.71	Higher rates of low thrombocyte count among the cases (p=0.0071)
6	Choręziak et al. (2019)	Retrospective	76 infants receiving ROP management and 87 patients with ROP spontaneous regression	25±1.72	830±206	-	39.5	32.2	Higher rates of low thrombocyte count among the cases (p=0.015)
7	Özkaya (2022)	Retrospective	40 infants with type 1 ROP and 40 premature infants without ROP	26.5 (24–32)	925 (430–1440)	<150,000	25	10	Non-significant difference in the platelet counts between infants with ROP and premature infants without ROP (p=0.094)
8	Gaber et al. (2021)	Retrospective cross-sectional	240 premature infants	33.25±2.74	1955.23±692.43	-			Low thrombocyte counts as a risk factor for ROP (OR=2.0 (0.6-6.5))
9	Yau et al. (2015)	Retrospective cross-sectional	153 multiple-gestation infants	30.8±2.4	1284.8±267.4	-			OR=1.76; p=0.57 (not significant)

Five studies conducted by Sancak et al. (2019), Lundgren et al. (2017), Parrozzani et al. (2021), Choręziak et al. (2019), and Özkaya (2022) have documented low thrombocyte counts in infants diagnosed with ROP. The prevalence of thrombocytopenia among the research subjects ranged from 18.37% to 71%. These results indicated that preterm infants without ROP might also have decreased thrombocyte counts, affecting approximately 5.71% to 21% of the cases.

Seven studies conducted by Sancak et al. (2019), Cakir et al. (2018), Jensen et al. (2018), Gaber et al. (2021), Yau et al. (2015), Parrozzani et al. (2021), and Lundgren et al. (2017) have identified low thrombocyte counts as a significant risk factor for ROP. The range of the odds ratio (OR) for thrombocytopenia was found to be between 2.8 and 6.69. Most of these studies compared the occurrence of low thrombocyte counts between premature infants with type 1 ROP and premature newborns without ROP. The results of the studies revealed a significant relationship between the two conditions. However, thrombocytopenia did not appear to have any discernible effect on ROP, according to the analysis of zone 2 ROP. This was specifically apparent in newborns with a gestational age between 35 and 38 weeks, as well as between infants with stabilized ROP and those with progressive ROP.

DISCUSSION

ROP is a complex vasoproliferative condition affecting the retinas of premature infants born with inadequate vascularization. It has emerged as a significant newborn illness that causes about 40% of all childhood blindness worldwide. Advancements in neonatal care have led to an increase in the survival rate of infants with low birth weight, thereby increasing the incidence of ROP (Tan et al. 2022).

According to the comprehensive review in this study, thrombocytopenia increases the probability of ROP development in premature infants. However, the specific mechanism by which thrombocytopenia impacts the progression of ROP and the balance of VEGF remains unknown. Existing studies have highlighted the crucial regulatory function of angiogenic factors, such as insulin-like growth factor 1 (IGF-1) and VEGF. Platelets transport, store, and release both of these angiogenic factors (Sancak et al. 2019, Dai et al. 2021, Guo et al. 2021).

There are two phases in the pathogenesis of ROP. High oxygen levels in the uterus during the first phase decrease retinal VEGF expression. This mechanism prevents the interference of blood in the growth of blood vessels, which results in the constriction of retinal capillaries and the formation of avascular regions in the retina. During the second phase, the infant experiences relative hypoxia, which subsequently triggers the upregulation of VEGF by Müller cells and astrocytes. The surge in VEGF expression results in neovascularization in the retina, which is a pathognomonic feature of ROP (Guo et al. 2021).

Proliferative retinopathy has been associated with increased production of endogenous IGF-1, which is a consequence of retinal VEGF accumulation during the second phase of ROP pathogenesis. Therefore, thrombocytopenia may contribute to insufficient VEGF sequestration in the developing retina, subsequently leading to the onset or progression of proliferative retinopathy. Examinations of platelet counts and the related factors are relevant in both the first and second phases of ROP. Numerous studies investigating ROP pathogenesis in the first phase did not uncover significant differences in thrombocyte parameters. Therefore, it might indicate that platelets exhibited heightened activity. Meanwhile, in the second phase, the platelets could induce a rise in neovascularization. Certain studies among the chosen literature only included the second phase, while other studies included both the first and second phases. However, the precise function of platelets in regulating VEGF has not been well understood (Cakir et al. 2018).

The impact of thrombocytopenia on APROP has been investigated previously. A large discrepancy was observed in the platelet counts between infants diagnosed with APROP and those without the disease. Platelet transfusions helped alleviate thrombocytopenia in a severely ill patient experiencing spontaneous regression of APROP by increasing the platelet count from 21,000/mm^3 to 118,000/mm^3. In a separate setting with 21 controls and 9 APROP cases, there was a significant difference in thrombocyte counts between patients with APROP and the control participants. Low platelet counts can hinder the ability of preterm children with APROP to effectively regulate the excessive production of VEGF caused by peripheral retinal ischemia and maintain optimal VEGF levels (Seliniotaki et al. 2022).

Platelet transfusions were found to prevent vascularization in mouse animal models of oxygen-induced retinopathy. Mice affected by retinopathy had lower platelet counts compared to those grown in normal conditions. Platelet depletion in mouse models of ROP resulted in an increase in the formation of abnormal blood vessels in the retina, known as neovascular tufts. Conversely, platelet transfusion exerted the opposite effect by decreasing the formation of neovascular tufts. A statistically significant difference was observed in the average

weekly platelet counts of the mice, distinguishing those with severe ROP from those with no or milder ROP (Cakir et al. 2018).

Thrombocytopenia is a common hematologic condition in newborns that can cause death and morbidity. It affects approximately 1-5% of all newborns, 12% of preterm infants, and 20–40% of infants receiving intensive care. Thrombocytopenia becomes more common as gestational age and body weight decrease. A decrease in thrombocyte count can contribute to the development of ROP by disrupting the optimum balance of angiogenesis-regulating substances, such as VEGF, endostatin, and thromboxane A2. The results of this study aligned with recent research, which observed a correlation between severe ROP and thrombocytopenia (Şahinoğlu Keşkek et al. 2020, Seliniotaki et al. 2022).

Several studies conducted by Cakir et al. (2018), Sancak et al. (2019), and Kumawat et al. (2021) have found that thrombocytes have an anti-angiogenic effect on the formation of the retina. This occurs due to the removal of excess VEGF during the vascularization stage. Thus, thrombocytopenia is associated with a more severe form of ROP. In addition, there is a correlation between thrombocytopenia and low levels of VEGF-A (Lundgren et al. 2017).

Platelets are recognized as having a storage and transportation system for various pro- and anti-angiogenic regulators. The regulators include insulin-like growth factor binding protein (IGFBP-3), which serves as the primary serum binding protein for IGF-1, VEGF, and platelet-derived growth factor (PDGF). Each of these regulators is present within the alpha granules of platelets. It was observed that severe thrombocytopenia improved significantly following the administration of serum platelet transfusions to a patient with APROP. Furthermore, a correlation was discovered between thrombocytopenia and type 1 ROP in zone 1. These findings suggest that thrombocytopenia can be considered a risk factor for zone 1 ROP (Holinstat 2017, Cakir et al. 2018).

Platelets contain three distinct types of secretory granules that store bioactive molecules. These components include dense granules, alpha-granules, and lysosomes. Among these granules, the most common ones are angiostatin, platelet factor 4, thrombospondin 1, 2-macroglobulin, endostatin, and plasminogen activator inhibitor 1. Although platelets contain both pro- and anti-angiogenic substances, previous studies have mostly focused on investigating the pro-angiogenic or pro-proliferative properties of platelets when analyzing their effects on endothelial cells (Rubio & Adamis 2016, Sharda & Flaumenhaft 2018).

A study discovered a correlation between severe ROP and thrombocytopenia occurring from birth to a postmenstrual age (PMA) of 34 weeks. None of the newborns in the study required platelet transfusions, and their platelet counts did not decrease to levels that indicate thrombocytopenia. However, significant differences in platelet counts were observed between infants who developed ROP and those who did not. Platelets have a pivotal role in regulating angiogenic factors, such as VEGF and PDGF. The regulation is possible through the storage, transportation, and release of these factors. Therefore, platelets can serve as crucial regulators for the aforementioned proteins (Jensen et al. 2018, Özkaya 2022).

Strength and limitations

The main strength of this study was that it was regarded as the first comprehensive review of the relationship between ROP and thrombocytopenia. In contrast to previous studies that included only a limited scope of research, this study incorporated a wider range of research. However, it is important to take into account a few drawbacks of this study. Two of the studies included in this systematic review were cross-sectional, while the rest were retrospective. This might affect the reliability and validity of the evidence presented. The study populations were diverse, while thrombocytopenia is characterized by a certain threshold of platelet count that can differ across individuals. Additionally, different centers might have used various instruments to evaluate platelets, potentially leading to variations in diagnosis accuracy across studies. Certain selected studies failed to properly control the confounding variables, which could result in over- or underestimations of the findings.

CONCLUSION

Thrombocytopenia may play a role as a risk factor in the development of retinopathy of prematurity (ROP). Low thrombocyte levels in premature infants have the potential to serve as a clinical biomarker for type 1 ROP detection. However, further research is required to determine the critical platelet count threshold for ROP.

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Conflict of interest

None.

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None.

Author contribution

IWES contributed to the conception and design. NMAS contributed to the conception and design as well as the analysis and interpretation of the data. PAA contributed to the drafting of the article, critical revision of the article for important intellectual content, and collection and assembly of data. PD contributed to the drafting of the article as well as the collection and assembly of data. SA contributed to the drafting of the article as well as the collection and assembly of data.

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