Effect of red blood cell transfusion on the development of retinopathy of prematurity: A systematic review and meta-analysis

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Abstract

Background
The effect of red blood cell (RBC) transfusion on retinopathy of prematurity (ROP) is difficult to establish, because ROP may also be influenced by other factors. Therefore, we carried out a systematic review and meta-analysis to explore the relationship between RBC transfusion and the development of ROP.

Methods
The PubMed, Embase, Cochrane Library and Web of Science databases were searched from their inception to September 1, 2019. Observational studies that reported the relationship between RBC transfusion and ROP after adjusting for other potential risk factors were included. The combined result was analyzed by a random effect model. Heterogeneity and publication bias were tested, and sensitivity analysis was performed.

Results
Of the 2628 identified records, 18 studies including 15072 preterm infants and 5620 cases of ROP were included. A random effect model was used and revealed that RBC transfusion was significantly associated with ROP (pooled OR = 1.50, 95% CI: 1.27–1.76), with moderate heterogeneity among the included studies ($I^2 = 44.2\%$). Subgroup analysis indicated that RBC transfusion was more closely related to ROP in the group with a gestational age (GA) $\leq 32$ weeks (OR = 1.77, 95% CI: 1.29–2.43) but not in the groups with a GA $\geq 34$ weeks (OR = 1.36, 95% CI: 0.85–2.18) or a GA $< 37$ weeks (OR = 1.25, 95% CI: 0.86–1.82). No obvious publication bias was found based on the funnel plot and Egger’s test. Removing any single study did not significantly alter the combined result in the sensitivity analysis.
Conclusions
Our study revealed that RBC transfusion is an independent risk factor for the development of ROP, especially in younger preterm infants. However, there seemed to be no evidence to support an effect of RBC transfusion on ROP in older groups. Further studies addressing this issue in older preterm neonates are warranted.

Introduction
Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the retinas of preterm infants and is the leading cause of childhood blindness worldwide [1]. ROP is affected by multiple factors, such as maternal, perinatal, infant and treatment factors, and among these factors, red blood cell (RBC) transfusion may play an important role [2].

Due to the immature hematopoietic system and iatrogenic phlebotomy losses, preterm infants frequently undergo transfusion [3]. Reports have found that approximately 90% of extremely low birth weight (ELBW) infants receive at least one RBC transfusion [3]. In general, RBC transfusion is able to improve anemia, increase tissue oxygenation, promote growth and reduce mortality [4, 5]. However, considerable evidence suggests that RBC transfusion is related to several preterm disorders, including the development of ROP [5]. According to a national survey by Ludwig [6], the incidence of ROP in the transfusion group was 1.68-times as high as that in the non-transfusion group. Other studies did not identify a close relationship between RBC transfusion and ROP, especially after adjusting for other risk factors [7, 8]. Moreover, the most severely ill infants receive more RBC transfusions [9], making it difficult to identify the effect of RBC transfusion on ROP.

Therefore, a systematic review and meta-analysis was carried out to investigate the effect of RBC transfusion on the development of ROP. Because other risk factors may make it difficult to identify the role of RBC transfusion in ROP, only original studies reporting a relationship between RBC transfusion and ROP after adjusting for other potential risk factors were included.

Materials and methods
Search strategy
This systematic review and meta-analysis was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [10, 11]. The PubMed, Embase, Cochrane Library and Web of Science databases were searched from their inception to September 1, 2019. The search was performed using combinations of the following keywords: “preterm infants”, “red blood cell transfusion” and “retinopathy of prematurity” without language limitation. The detailed search strategy for PubMed is shown in S1 Table. Moreover, reference lists from the key articles were also searched manually.

Inclusion and exclusion criteria
The inclusion criteria included the following: (1) Original studies that reported the adjusted odds ratio (OR) and 95% confidence interval (CI) between RBC transfusion (yes or no) and any stage of ROP after adjusting for other potential confounding risk factors and (2) observational studies, including case-control and cohort studies. Duplicate studies, review articles,
case reports, letters to editors, conference abstracts and articles with no available data were excluded.

Data extraction
Two reviewers (ZZ and XH) independently selected studies and extracted data using a form that included study design, area, publication year, sample size, the main inclusion criteria, exposures and outcomes. If disagreements occurred, they were resolved by the third reviewer (PZ).

Quality assessment
The Newcastle-Ottawa Scale was selected to assess the quality of the included studies. This scale, with a maximum of 9 points, is made up of three parts: patient selection (4 points), comparability of the study groups (2 points) and exposure/outcome (3 points). A study with a score below 6 points was considered to be of low quality.

Statistical analysis
This meta-analysis was performed using Stata 16.0 software (StataCorp LP, College Station, Texas). Adjusted ORs with 95% CIs from the included studies were extracted, and the combined result was analyzed by using a random effect model with the DerSimonian–Laird method and displayed on forest plots. Heterogeneity was assessed using the chi-square test, and $I^2$ was calculated; $I^2$ values of 25%, 50%, and 75% indicated low, moderate and high heterogeneity [12]. Predefined subgroup analyses were performed according to study design, sample size, GA area, and year of publication. Moreover, we used funnel plots and Egger’s test to examine publication bias and utilized sensitivity analysis to assess the stability of the combined result.

Results
Search results and characteristics of eligible studies
A total of 2628 records were retrieved from the electronic and manual search. After duplicate removal, abstract screening and full-text article review, 18 studies with 15072 preterm infants and 5620 cases of ROP were included in this meta-analysis (Fig 1). The characteristics of the eligible studies are shown in Table 1. The NOS scores of the included studies ranged from 6 to 8, and detailed information is shown in S2 Table.

Effects of RBC transfusion on ROP
Fig 2 shows the pooled results of 18 studies assessed using a random effect model, which indicated that RBC transfusion had a close relationship to ROP (pooled OR = 1.50, 95% CI: 1.27–1.76), with moderate heterogeneity among the included studies ($I^2 = 44.2\%, 95\%$ CI: 2.7%–67.9%).

Subgroup analysis
High heterogeneity was shown in studies conducted in the North American area ($P = 0.027, I^2 = 79.5\%$). Elevated risks were identified in studies with a cohort design, with a sample size $\geq 600$, with a GA $\leq 32$ weeks, conducted in South America and from published 2015–2019, with ORs of 1.56 (95% CI: 1.30–1.88), 1.52 (95% CI: 1.27–1.83), 1.77 (95% CI: 1.29–2.43), 2.44 (95% CI: 1.56–3.81) and 1.55 (95% CI: 1.27–1.90), respectively. However, there seemed to be
no strong evidence to support an effect of RBC transfusion on ROP in case-control studies, studies performed in North America or studies that screened infants with a GA $\leq 34$ weeks or $<37$ weeks, with ORs of 1.24 (95% CI: 0.81–1.90), 1.11 (95% CI: 0.51–2.43), 1.36 (95% CI: 0.85–2.18), and 1.25 (95% CI: 0.86–1.82), respectively (Fig 3).

Publication bias and sensitivity analysis

Fig 4 shows the funnel plot of the studies included in this meta-analysis, and Egger’s test revealed a value of 1.11 ($P = 0.287$), which implied no obvious publication bias.

No apparent change was found in the pooled OR when any single study was removed, with a range from 1.44 (95% CI: 1.23–1.68) to 1.54 (95% CI: 1.28–1.86).

Discussion

In this systematic review and meta-analysis, 13 cohort and 5 case-control studies including 15072 preterm infants and 5620 cases of ROP were included; among these studies, 10 indicated that RBC transfusion was significantly associated with ROP after adjusting for other confounding factors [13–18, 23–26], while others did not demonstrate this association [7, 8, 19–22, 27, 28]. Combining all of these studies, we found that RBC transfusion played a driving role in the development of ROP in preterm infants, with a pooled OR of 1.50 (95% CI: 1.27–1.76). Moderate heterogeneity was shown among the included studies ($P = 0.023, I^2 = 44.2\%$). No apparent publication bias was found according to the evaluation of the funnel plot and Egger’s test.

A subgroup analysis of case-control studies showed that there was no significant relationship between RBC and ROP (OR = 1.24, 95% CI: 0.81–1.90). The inclusion of few studies and the small sample size (5 studies including 2253 preterm infants and 650 ROP cases) may
| Author             | Year of publication | Sample size | ROP cases | Included criteria | Area       | Study design | Adjusted OR (95% CI) | Adjustments                                                                                                                                                                                                                                                                                                                                 |
|--------------------|---------------------|-------------|-----------|-------------------|------------|--------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zarei [13]         | 2019                | 1990        | 575       | GA <37 weeks      | Iran       | cohort       | 1.355 (1.001–1.833) | GA, BW, gender, multiple gestation, oxygen therapy, IVP, sepsis, RDS, phototherapy, Intubation                                                                                                                                                                                                                     |
| Akkawi [7]         | 2019                | 115         | 27        | BW <1500 g, GA ≤32 weeks | Palestine | case-control | 2.642 (0.66–10.567) | GA, BW, multiple gestation, sibling affected by ROP, Hb at birth, RDS, lowest Hb, maximum bilirubin, days on mechanical ventilation, days on non-mechanical ventilation, days on oxygen therapy                                                                                                                                 |
| Wu [14]            | 2018                | 504         | 131       | BW <1500 g        | China      | cohort       | 1.819 (1.043–3.163) | GA, BW, pregnancy induced hypertension, premature rupture of membranes, intrauterine growth retardation, congenital pneumonia, anemia, sepsis, NEC, shock, birth asphyxia, hyaline membrane disease, surfactant, continuous positive airway pressure, phototherapy, oxygen therapy >7 days, ventilator |
| Sathar [15]        | 2018                | 812         | 203       | BW <1500 g, GA ≤32 weeks | India    | cohort       | 2.567 (1.456–4.528) | BW <1500g GA, pregnancy induced hypertension, premature rupture of membranes, intrauterine growth retardation, congenital pneumonia, anemia, sepsis, NEC, shock, birth asphyxia, hyaline membrane disease, surfactant, continuous positive airway pressure, phototherapy, oxygen therapy >7 days, ventilator |
| Alshaikh [16]      | 2017                | 282         | 76        | BW <1500g, GA <31 weeks | Canada    | cohort       | 1.567 (1.198–2.04)  | GA, BW, SNAP-PE score, oxygen therapy days, ventilator days, caesarean section, Caucasian, chorioamnionitis, gender, IUGR, RDS, PDA, surfactant use, sepsis, IVH, NEC, BPD                                                                                                                                 |
| Yau [8]            | 2016                | 513         | 95        | BW <1500 g, GA ≤32 weeks | Hong Kong | case-control | 1.28 (0.18–13.17)   | GA, BW, preeclampsia, gestational diabetes mellitus, IVF, postnatal hypotension, inotrope use, BPD, surfactant use, invasive mechanical ventilation, mean oxygen concentration, patent ductus arteriosus, NSAID use, anemia, IVH, hypoglycemia                                                                                                                                 |
| Huang [17]         | 2015                | 5718        | 2785      | BW <1500 g        | Taiwan     | cohort       | 1.26 (1.11–1.44)    | preeclampsia, GA, BW, cesarean section, gender, GSA, Apgar score, RDS, PDA, sepsis                                                                                                                                                                                                                     |
| Ezz El Din [18]    | 2015                | 111         | 21        | BW <1500 g, GA ≤32 weeks | Egypt     | cohort       | 6.11 (1.22–30.44)   | GA, BW, Gender, positive consanguinity, multiple gestation, vaginal delivery, maternal diabetes, maternal hypertension, PPROM, RDS, neonatal jaundice, IUGR, duration of admission, oxygen, ventilation, duration of ventilation, feeding, anemia, pneumothorax, BPD, PDA, inotropes, duration of inotropes, NEC, IVH, anemia, thrombocytopenia, sepsis, candida sepsis |
| Rao [19]           | 2013                | 282         | 61        | BW <1500 g, GA ≤32 weeks | India     | cohort       | 1.37 (0.48–3.96)    | GA, BW, surfactant, sepsis, anemia, IPPV                                                                                                                                                                                                                     |
| Küçükevlioglu [20] | 2013                | 640         | 240       | BW <1501 g, GA ≤34 week | Turkey    | cohort       | 1.508 (0.892–2.552) | GA, BW, oxygen therapy, mechanical ventilation, RDS, sepsis, IVH                                                                                                                                                                                                                     |
| Isaza [21]         | 2013                | 423         | 171       | BW <1500 g, GA ≤32 weeks | Canada    | cohort       | 0.7 (0.36–1.36)     | GA, BW, gender, days on ventilation therapy, perinatal infection, IVH, PDA, NEC                                                                                                                                                                                                                     |
| Akçakaya [22]      | 2012                | 517         | 177       | GA <37 weeks     | Turkey     | case-control | 0.651 (0.333–1.274) | GA, BW, sepsis, oxygen therapy, RDS, mechanical ventilation                                                                                                                                                                                                                     |
| Fortes [23]        | 2011                | 324         | 97        | BW <1500 g, GA ≤32 weeks | Brazil    | cohort       | 2.901 (1.533–5.49)  | GA, maternal preeclampsia, antenatal steroid treatment, essential hypertension, IVH, use of oxygen in mechanical ventilation, use of indomethacin, vaginal delivery, SGA                                                                                                                                 |

(Continued)
partially explain this. Another reason may relate to the included criteria, as 2 of the 5 case-control studies screened preterm infants with GA < 37 weeks [29, 30]. This was confirmed in
Fig 3. Subgroup analyses according to different study design, sample size, GA area and year of publication. GA: gestational age.

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Fig 4. Funnel plot for the association between RBC transfusion and the development of ROP. RBC: red blood cell, ROP: Retinopathy of prematurity, or: odd ratio, s.e.: standard error.

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another subgroup study performed by GA, which showed that the risk of ROP attributed to RBC transfusion increases as GA decreases, with ORs of 1.77 (95% CI: 1.29–2.43) in the GA ≤ 32 weeks group, 1.36 (95% CI: 0.85–2.18) in the GA ≤ 34 weeks group and 1.25 (95% CI: 0.86–1.82) in GA < 37 weeks group. There seemed to be no evidence to support an effect of RBC transfusion on ROP, which included older preterm infants in this meta-analysis. Previous studies have reported that the younger the preterm newborn is, the more frequently he or she requires transfused blood products [4, 31], and RBC transfusion times were associated with an increased risk of ROP [32, 33]. This phenomenon may suggest that the immature retina of younger infants is more susceptible to RBC transfusion effects.

ROP is a multifactorial disease, and one of the key elements in its development is oxidative damage [1], which is exactly what RBC transfusion results in. RBC transfusion influences ROP mainly in two ways. First, RBC transfusion increases iron intake, thereby increasing the level of its oxidation product. As early as 1997, Inder et al [34] discovered a close relationship between RBC transfusion, excessive iron load and ROP. Hirano's study, in favor of such a view, further noticed that the same situation did not appear in full-term infants [35]. Second, unlike fetal hemoglobin (HbF), adult hemoglobin (HbA) has a lower affinity for oxygen, thereby shifting the oxygen-hemoglobin dissociation curve to the right and unloading more oxygen to the developing retina after the transfusion of adult blood products [5]. In a pilot prospective cohort study, Stutchfield et al [36] demonstrated that lower %HbF caused by transfusion is an independent risk factor for ROP. Additionally, biologically active substances in blood products may also play a role [5].

RBC transfusion is a life-saving therapeutic method in some emergency conditions, but it is known to inhibit the immune response and transmit infectious diseases [4]. Our findings again call upon doctors to weigh the risks of RBC transfusions against the benefits. Neonatologists have adopted several methods to reduce RBC transfusion in preterm infants. A systematic review and meta-analysis [37] demonstrated that the use of restrictive hemoglobin thresholds would reduce transfusion but had no significant impact on death or major morbidities. Other strategies include delayed cord clamping [38], milking of the umbilical cord [39] and autologous or allogenic umbilical cord blood transfusion [40, 41].

The strength of this meta-analysis was that it combined 18 observational studies that reported the effect of RBC transfusion on ROP after adjusting for other confounding risk factors. Limitations included the potential influence of different confounders and heterogeneity among the included studies. First, the confounders varied between different studies; some studies performed fully adjusted analyses, while others performed partially adjusted analyses. Moreover, maternal factors such as preeclampsia [42] and maternal diabetes [43] were seldom included as potential confounders in these studies. Second, moderate heterogeneity was found among the included studies. Third, although no obvious publication bias was found by funnel plot and Egger’s test, the number of studies included in this meta-analysis was still insufficient to make a certain assessment about the publication bias. These limitations must be considered when interpreting the final results.

Conclusions

In conclusion, this systematic review and meta-analysis reveals that RBC transfusion is an independent risk factor for the development of ROP, especially in younger preterm infants. This calls upon doctors to weigh the risks of RBC transfusion against the benefits and avoid unnecessary transfusion in preterm infants. However, there seemed to be no evidence to support an effect of RBC transfusion on ROP in older groups. Further studies addressing this issue in older preterm neonates are warranted.
Supporting information
S1 Table. PubMed search strategy. (DOCX)
S2 Table. The Newcastle-Ottawa Scale of included studies. (DOCX)
S1 Checklist. PRISMA checklist. (DOC)

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References
1. Hartnett ME. Advances in understanding and management of retinopathy of prematurity. Survey of ophthalmology. 2017; 62(3):257–76. Epub 2016/12/26. https://doi.org/10.1016/j.survophthal.2016.12.004 PMID: 28012875; PubMed Central PMCID: PMC5401801.
2. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Survey of ophthalmology. 2018; 63(5):618–37. Epub 2018/04/22. https://doi.org/10.1016/j.survophthal.2018.04.002 PMID: 29679617; PubMed Central PMCID: PMC6089661.
3. Strauss RG. Anaemia of prematurity: pathophysiology and treatment. Blood Rev. 2010; 24(6):221–5. Epub 2010/09/08. https://doi.org/10.1016/j.blre.2010.08.001 PMID: 20817366; PubMed Central PMCID: PMC2981681.
4. Howarth C, Banerjee J, Aladangady N. Red Blood Cell Transfusion in Preterm Infants: Current Evidence and Controversies. Neonatology. 2018; 114(1):7–16. Epub 2018/03/20. https://doi.org/10.1159/000486584 PMID: 29550819.
5. Crawford TM, Andersen CC, Hodyl NA, Robertson SA, Stark MJ. The contribution of red blood cell transfusion to neonatal morbidity and mortality. Journal of paediatrics and child health. 2019; 55(4):387–92. Epub 2019/02/10. https://doi.org/10.1111/jpc.14402 PMID: 30737649.
6. Ludwig CA, Chen TA, Hernandez-Boussard T, Moshfeghi AA, Moshfeghi DM. The epidemiology of retinopathy of prematurity in the United States. Ophthalmic Surgery Lasers and Imaging Retina. 2017; 48(7):553–62. https://doi.org/10.3928/23258160-20170630-06 PMID: 28728176.
7. Akkawi MT, Shehadeh MM, Shams ANA, Al-Hardan DM, Omar LJ, Almahmoud OH, et al. Incidence and risk factors of retinopathy of prematurity in three neonatal intensive care units in Palestine. BMC ophthalmology. 2019; 19(1):189. Epub 2019/08/21. https://doi.org/10.1186/s12886-019-1180-4 PMID: 31429728; PubMed Central PMCID: PMC6701108.
8. Yau GS, Lee JW, Tam VT, Liu CC, Yip S, Cheng E, et al. Incidence and Risk Factors of Retinopathy of Prematurity From 2 Neonatal Intensive Care Units in a Hong Kong Chinese Population. Asia-Pacific
A meta-analysis of the association between red blood cell transfusion and retinopathy of prematurity

journal of ophthalmology (Philadelphia, Pa). 2016; 5(3):185–91. Epub 2016/05/18. https://doi.org/10.1097/ apo.000000000000167 PMID: 27183289.

9. Christensen RD, Istrup SJ, Hartnett ME. Retinopathy of prematurity and transfusion practice. Transfusion. 2014; 54(4):960–1. Epub 2014/04/15. https://doi.org/10.1111/trf.12510 PMID: 24724787.

10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000; 283(15):2008–12. Epub 2000/05/02. https://doi.org/10.1001/jama.283.15.2008 PMID: 10789670.

11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7):e1000097. Epub 2009/07/22. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072; PubMed Central PMCID: PMC2707599.

12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. Epub 2003/09/06. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120; PubMed Central PMCID: PMC192859.

13. Zarei M, Bazvand F, Ebrahimimadib N, Roohpoor R, Karkhanesh R, Dastjani AF, et al. Prevalence and Risk Factors of Retinopathy of Prematurity in Iran. Journal of ophthalmic & vision research. 2019; 14(3):291–8. https://doi.org/10.18502/jovr.v14i3.4785 PMID: 31660108 PubMed PMID: WOS:000478797000008.

14. Wu T, Zhang L, Tong Y, Qu Y, Xia B, Mu D. Retinopathy of Prematurity Among Very Low-Birth-Weight Infants in China: Incidence and Perinatal Risk Factors. Investigative ophthalmology & visual science. 2018; 59(2):757–63. Epub 2018/02/03. https://doi.org/10.1167/iovs.17-23158 PMID: 29392321.

15. Sathar A, Shanavas A, Girjadevi PS, Jasmin LB, Pillai RK, Risk factors of retinopathy of prematurity in a tertiary care hospital in South India. Clinical Epidemiology and Global Health. 2018; 6(1):44–9. https://doi.org/10.1016/j.cejgh.2017.02.002 PubMed PMID: WOS:000428022000009.

16. Alishaik B, Salman O, Soliman N, Ellis A, Yusuf K. Pre-eclampsia and the risk of retinopathy of prematurity in preterm infants with birth weight <1500 g and/or <31 weeks' gestation. BMJ open ophthalmology. 2017; 1(1):e000049. Epub 2018/01/23. https://doi.org/10.1136/bmjophthal-2016-000049 PMID: 29354703; PubMed Central PMCID: PMC5721629.

17. Huang HC, Yang HI, Chou HC, Chen CY, Hsieh WS, Tsou KI, et al. Preeclampsia and Retinopathy of Prematurity in Very-Low-Birth-Weight Infants: A Population-Based Study. PloS one. 2015; 10(11). https://doi.org/10.1371/journal.pone.0143248 PMID: 26588850 PubMed PMID: WOS:000365251500042.

18. Ezz El Din ZM, El Sada MA, Ali AA, Al Husseiny K, Yousef AAR. Comparison of Digital Imaging Screening and Indirect Ophthalmoscopy for Retinopathy of Prematurity. Indian journal of pediatrics. 2015; 82(1):80–3. https://doi.org/10.1007/s12098-014-1525-1 PMID: 25081804.

19. Rao KA, Purkayastha J, Hazarika M, Chaitra R, Mithun Adith K. Analysis of prenatal and postnatal risk factors of retinopathy of prematurity in a tertiary care hospital in South India. Indian journal of ophthalmology. 2013; 61(11):640–4. https://doi.org/10.4103/0301-4738.119347 PMID: 24145565.

20. Küçükkevecilloğlu M, Mutlu FM, Sarici SU, Ceylan OM, Altninsky HI, Kilic S, et al. Frequency, risk factors and outcomes of retinopathy of prematurity in a tertiary care hospital in Turkey. Turkish Journal of Pediatrics. 2013; 55(5):467–74. PMID: 23482326.

21. Isaza G, Arora S, Bal M, Chaudhary V. Incidence of retinopathy of prematurity and risk factors among premature infants at a neonatal intensive care unit in Canada. Journal of pediatric ophthalmology and strabismus. 2013; 50(1):27–32. Epub 2012/12/05. https://doi.org/10.3928/01913913-20121127-02 PMID: 23205771.

22. Açıkgöz A, Yaylali SA, Erbil HH, Sadigov F, Aybar A, Aydin N, et al. Screening for retinopathy of prematurity in a tertiary hospital in Istanbul: Incidence and risk factors. Journal of pediatric ophthalmology and strabismus. 2012; 49(1):21–5. https://doi.org/10.3928/01913913-20121020-01 PMID: 21323244.

23. Fortes JB, Costa MC, Eckert GU, Santos PGB, Silveira RC, Prociannon RS. Maternal Preeclampsia Protects Preterm Infants against Severe Retinopathy of Prematurity. Journal of Pediatrics. 2011; 158(3):372–6. https://doi.org/10.1016/j.jpeds.2010.08.051 PMID: 20885573 PubMed PMID: WOS:000287231800007.

24. Zhu L, Shi WJ, Zhang SL, Yu LP, Yao MZ, Shi YY, et al. Evaluation of risk factors for retinopathy of prematurity. Zhonghua yi xue za zhi. 2011; 91(25):1749–52. Epub 2011/11/19. PMID: 22093732.

25. Figueras-Aloy J, Álvarez-Domnguez E, Morales-Ballus M, SalviJa-Rojges MD, Moretones-Suñol G. Early administration of erythropoietin in the extreme premature, a risk factor for retinopathy of prematurity? Anales de Pediatría. 2010; 73(6):327–33. https://doi.org/10.1016/j.anpedi.2010.09.001 PMID: 20951656
26. Pinheiro AM, Silva WA, Bessa CG, Cunha HM, Ferreira MA, Gomes AH. Incidence and risk factors of retinopathy of prematurity in University Hospital Onofre Lopes, Natal (RN)-Brazil. Arquivos brasileiros de oftalmologia. 2009; 72(4):451–6. Epub 2009/10/13. https://doi.org/10.1590/s0004-27492009000400005 PMID: 19820782.

27. Mutlu FM, Altinsoy HI, Mumucuoglu T, Kerimoglu H, Kılıç S, Kul M, et al. Screening for retinopathy of prematurity in a tertiary care newborn unit in Turkey: Frequency, outcomes, and risk factor analysis. Journal of pediatric ophthalmology and strabismus. 2008; 45(5):291–8. https://doi.org/10.3928/01913913-20080901-12 PMID: 18825902.

28. Kim TI, Sohn J, Pi SY, Yoon YH. Postnatal risk factors of retinopathy of prematurity. Paediatric and perinatal epidemiology. 2004; 18(2):130–4. Epub 2004/03/05. https://doi.org/10.1111/j.1365-3016.2003.00545.x PMID: 14996252.

29. Akcakaya AA, Yaylali SA, Erbil HH, Sadigov F, Aybar A, Aydin N, et al. Screening for retinopathy of prematurity in a tertiary hospital in Istanbul: incidence and risk factors. Journal of pediatric ophthalmology and strabismus. 2012; 49(1):21–5. Epub 2011/02/18. https://doi.org/10.3928/01913913-20110208-01 PMID: 21329244.

30. Kim TI, Sohn J, Pi SY, Yoon YH. Postnatal risk factors of retinopathy of prematurity. Paediatric and perinatal epidemiology. 2004; 18(2):130–4. https://doi.org/10.1111/j.1365-3016.2003.00545.x PMID: 14996252.

31. Ghirardello S, Duai E, Cortinovis I, Villa S, Furnagalli M, Agosti M, et al. Effects of Red Blood Cell Transfusions on the Risk of Developing Complications or Death: An Observational Study of a Cohort of Very Low Birth Weight Infants. American journal of perinatology. 2017; 34(4):88–95. Epub 2016/06/02. https://doi.org/10.1056/s-0036-1584300 PMID: 27249797.

32. Yum SK, Moon CJ, Youn YA, Lee JH, Kim SY, Sung IK. Expanded criteria for retinopathy of prematurity screening in moderately preterm infants: Single-center pilot study. Pediatrics international: official journal of the Japan Pediatric Society. 2016; 58(11):1158–62. Epub 2016/04/03. https://doi.org/10.1111/pedi.12996 PMID: 27038039.

33. Thomas K, Shah PS, Canning R, Harrison A, Lee SK, Dow KE. Retinopathy of prematurity: Risk factors and variability in Canadian neonatal intensive care units. Journal of neonatal-perinatal medicine. 2015; 8(3):207–14. Epub 2015/10/21. https://doi.org/10.3233/NPM-15814128 PMID: 26485554.

34. Inder TE, Clemett RS, Austin NC, Graham P, Darlow BA. High iron status in very low birth weight infants is associated with an increased risk of retinopathy of prematurity. The Journal of pediatrics. 1997; 131(4):541–4. Epub 1997/12/05. https://doi.org/10.1016/s0022-3476(97)70058-1 PMID: 9386655.

35. Hirano K, Morinobu T, Kim H, Hiroi M, Ban R, Ogawa S, et al. Blood transfusion increases radical promoting non-transferrin bound iron in preterm infants. Archives of disease in childhood Fetal and neonatal edition. 2001; 84(3):F188–93. Epub 2001/04/26. https://doi.org/10.1136/fn.84.3.f188 PMID: 11320046; PubMed Central PMCID: PMC1721242.

36. Stutchfield CJ, Jain A, Odd D, Williams C, Markham R. Foetal haemoglobin, blood transfusion, and retinopathy of prematurity in very preterm infants: a pilot prospective cohort study. Eye (London, England). 2017; 8(3):207–14. Epub 2017/05/27. https://doi.org/10.1038/eye.2017.76 PMID: 28546851; PubMed Central PMCID: PMC5639193.

37. Whyte R, Kirpalani H. Low versus high haemoglobin concentration thresholds for blood transfusion for preventing morbidity and mortality in very low birth weight infants. The Cochrane database of systematic reviews. 2011; (11):CD005512. Epub 2011/11/11. https://doi.org/10.1002/14651858.CD005512.pub2 PMID: 22071798.

38. Rabe H, Gyte GM. Diaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. The Cochrane database of systematic reviews. 2010; 9:CD003248. Epub 2009/09/19. https://doi.org/10.1002/14651858.CD003248.pub4 PMID: 31529790; PubMed Central PMCID: PMC6748404.

39. March MJ, Hacker MR, Parson AW,MODEST AM, de Veciana M. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. Journal of perinatology: official journal of the California Perinatal Association. 2013; 33(10):763–7. Epub 2013/07/23. https://doi.org/10.1038/jp.2013.70 PMID: 23867960; PubMed Central PMCID: PMC3916936.

40. Kotowski M, Litwinska Z, Kloś P, Pius-Sadowska E, Zagrodnik-Ulan E, Ustianowski P, et al. Autologous cord blood transfusion in preterm infants—could its humoral effect be the key to control prematurity-related complications? A preliminary study. J Physiol Pharmacol. 2017; 68(6):921–7. Epub 2018/03/20. PMID: 29550804.

41. Bianchi M, Giannantonio C, Spartan S, Fioretti M, Landini A, Molisso A, et al. Allogeneic umbilical cord blood red cell concentrates: an innovative blood product for transfusion therapy of preterm infants. Neonatology. 2015; 107(2):81–6. Epub 2014/11/18. https://doi.org/10.1159/000368296 PMID: 25401961.
42. Shulman JP, Weng C, Wilkes J, Greene T, Hartnett ME. Association of Maternal Preeclampsia With Infant Risk of Premature Birth and Retinopathy of Prematurity. JAMA ophthalmology. 2017; 135 (9):947–53. Epub 2017/08/11. https://doi.org/10.1001/jamaophthalmol.2017.2697 PMID: 28796851; PubMed Central PMCID: PMC5710540.

43. Tunay ZO, Ozdemir O, Acar DE, Oztuna D, Uras N. Maternal Diabetes as an Independent Risk Factor for Retinopathy of Prematurity in Infants With Birth Weight of 1500 g or More. American journal of ophthalmology. 2016; 168:201–6. Epub 2016/06/12. https://doi.org/10.1016/j.ajo.2016.05.022 PMID: 27287819.