

# Analysis of Risk Factors in the Development of Retinopathy of Prematurity

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## SUMMARY

**Introduction** Retinopathy of prematurity (ROP) is a multifactorial disease that occurs most frequently in very small and very sick preterm infants, and it has been identified as the major cause of childhood blindness.

**Objective** The aim of this study was to evaluate ROP incidence and risk factors associated with varying degrees of illness.

**Methods** The study was conducted at the Centre for Neonatology, Paediatric Clinic of the Clinical Centre Kragujevac, Serbia, in the period from June 2006 to December 2008. Ophthalmologic screening was performed in all children with body weight lower than 2000 g or gestational age lower than 36 weeks. We analyzed eighteen postnatal and six perinatal risk factors and the group correlations for each of the risk factors.

**Results** Out of 317 children that were screened, 56 (17.7%) developed a mild form of ROP, while 68 (21.5%) developed a severe form. Univariate analysis revealed a large number of statistically significant risk factors for the development of ROP, especially the severe form. Multivariate logistical analysis further separated two independent risk factors: small birth weight ( $p=0.001$ ) and damage of central nervous system ( $p=0.01$ ). Independent risk factors for transition from mild to severe forms of ROP were identified as: small birth weight ( $p=0.05$ ) and perinatal risk factors ( $p=0.02$ ).

**Conclusion** Small birth weight and central nervous system damage were risk factors for the development of ROP, perinatal risk factors were identified as significant for transition from mild to severe form of ROP.

**Keywords:** retinopathy of prematurity; risk factors; multivariate statistical analysis

## INTRODUCTION

Retinopathy of prematurity (ROP) has been identified as the major cause of childhood blindness [1, 2]. In prematurely born babies, the retina is only partially formed [3]. The state of retina development is directly correlated to the severity of prematurity [4, 5].

Retinopathy of prematurity is a multifactorial disease that occurs most frequently in very small and very sick prematurely born babies [6, 7]. It has been believed for many years that oxygen therapy increases the risk of ROP in preterm infants [8]. However, ROP can occur even with careful control of oxygen therapy [9]. A number of risk factors have been implicated including low gestational age, low birth weight, increased number of blood transfusions [10], and the use of recombinant human erythropoietin as treatment for anaemia [11]. Other identified risk factors include sepsis, intraventricular haemorrhage [12] and mechanical ventilation [13].

## OBJECTIVE

The aim of this study was to evaluate ROP incidence and risk factors associated with varying degrees of illness.

## METHODS

In the period from June 2006 to December 2008, of 840 newborns admitted at the Centre for Neonatology of the Paediatric Clinic in Kragujevac, Serbia, 317 were screened for ROP. Screening was done in all newborns with birth weight (BW) < 2000 g, and/or gestational age (GA) < 36 gestational weeks (GW), as well as other newborns with severe diseases [4]. First ophthalmologic examination was conducted in the period between the third and the fifth week after birth. During the screening, findings were formulated in accordance with the International Classification of Retinopathy of Prematurity (ICROP) [14]. Children with ROP were treated according to the recommendations from the ETROP study [15, 16].

Screened patients were divided into three groups: Group A infants without ROP, Group B infants with milder form of ROP, and Group C infants with severe form of ROP treated with laser.

We analyzed the following post-natal risk factors: gender, GA, Apgar score (AS), BW, duration of oxygen therapy, duration of mechanical ventilation, number of transfusions, presence of sepsis, bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL)

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and patent ductus arteriosus (PDA). We also analyzed the effect of medications: surfactant, erythropoietin, vitamin E, diuretics, dopamine and dexamethasone administered before birth [17].

Gestational age was determined from the date of the last period and examination by the neonatologist. The oxygen therapy was monitored using pulse oximetry and did not exceed the level of 95% [18-22]. We could not influence the oxygenation of the infant in the delivery room nor during transport (since patients are delivered to intensive care unit from ten regional hospitals). Surfactant was administered to infants that fulfilled the clinical and radiological criteria for respiratory distress syndrome (RDSy). Antenatal steroid use was recommended for pregnancies between 24 to 34 weeks with threatened premature delivery to decrease the risk of RDSy [23].

Patent ductus arteriosus was diagnosed using echocardiographic examination. IVH and PVL were presented jointly as central nervous system (CNS). IVH and PVL were diagnosed with a series of ultrasound examinations of central nervous system. BPD was diagnosed based on the clinical and radiological lung exam, and a continued need for oxygen therapy past 36 post-conception weeks [24]. Erythropoietin was administered in the dosage of 200-250 IU/kg to infants in stable clinical condition, with GS less than 34 weeks after the second week of life. It was administered three times per week, with iron supplements, folic acid and vitamin E [28]. Vitamin E was administered after the second week of life to infants in stable clinical condition with BW less than 1500 g.

The following perinatal risk factors were also considered: premature rupture of foetal membranes, multiple pregnancies, chorioamnionitis, Caesarean section, EPH gestosis, and detachment of placenta.

Clinical data was subjected to statistical  $\chi^2$  test, univariate and multivariate regression analysis, and logistic regression. The  $\chi^2$  test was used to examine the differences in the frequency of individual risk factors among the screened patient groups. Multivariate regression was used to estab-

lish the predictors of development of ROP. Logistical regression was used to establish the predictors of development of ROP as well as the degrees of severity. The statistical software SPSS 15.0 was used in the analysis.

## RESULTS

Out of 317 screened patients, 125 (39.4%) were female and 192 (60.6%) male. The average value of GA was  $32.3 \pm 3.2$  GW (25 to 36). Average BW was  $1819.2 \pm 437.6$  g (700 to 2910 g). Screened patients were divided into three groups: Group A infants without ROP (60.9%), Group B infants with a mild form of ROP (17.7%), and Group C infants with a severe form of ROP treated with laser (21.5%). The analysis of the risk factors of the observed patient groups is given in Table 1.

Next we analyzed group correlations for each of the risk factors using univariate regression. In particular we analyzed the correlation of Group A with Group B, Group A with Group C, and Group B with Group C. Statistical significance factors for this analysis is shown in Table 2.

Gender was found to have no statistical significance among the screened groups. High statistical significance of GA was found in all three groups. With respect to the group of infants without ROP, GA of infants with severe form of ROP was four weeks higher. AS had high statistical significance only in groups of healthy infants and infants with severe form of ROP, which confirms that perinatal asphyxia is a significant risk factor for the development of severe form of ROP. Birth weight exhibited statistical significance in all three groups. Mechanical ventilation had a high statistical significance for several forms of ROP, especially severe ROP. The infants with severe form of ROP were kept on mechanical ventilation on average five times longer than healthy infants. BPD was also found to significantly affect the development of severe forms of ROP.

Oxygen therapy was found to be a risk factor with a high statistical significance for the development of both mild

**Table 1.** Retinopathy of prematurity risk factors analysis between three groups

Risk factors	Group A	Group B	Group C
Number of patients	193 (60.88%)	56 (17.66%)	68 (21.46%)
Gender (boys/girls)	120/73	30/26	42/26
Gestational weeks	$33.21 \pm 3.16$	$31.75 \pm 2.74$	$30.10 \pm 2.74$
Birth weight (g)	$1975.10 \pm 381.67$	$1738.66 \pm 408.43$	$1442.94 \pm 359.99$
Apgar score	$6.67 \pm 1.83$	$6.38 \pm 1.95$	$5.75 \pm 2.15$
Duration of mechanical ventilation (days)	$2.11 \pm 4.97$	$5.86 \pm 11.16$	$10.53 \pm 14.83$
Duration of oxygen therapy (days)	$13.94 \pm 10.60$	$22.82 \pm 22.24$	$33.97 \pm 22.26$
Dysplasia bronchopulmonalis	5 (2.59%)	9 (16.10%)	16 (23.5%)
Intraventricular haemorrhage	11 (5.70%)	8 (14.3%)	8 (11.80%)
Periventricular leucomalacia	104 (53.90%)	37 (66.1%)	56 (82.4%)
Sepsis	39 (20.20%)	19 (33.9%)	28 (41.17%)
Patent ductus arteriosus	10 (5.20%)	4 (7.11%)	8 (11.80%)
Number of blood transfusions	$1.24 \pm 1.49$	$2.46 \pm 2.19$	$3.95 \pm 3.08$
Erythropoietin	9 (4.70%)	8 (14.30%)	16 (23.50%)
Surfactant	22 (11.40%)	17 (30.40%)	31 (45.60%)
Diuretics	28 (14.50%)	19 (33.90%)	38 (55.90%)
Dopamine	14 (7.30%)	13 (23.20%)	26 (38.20%)
Vitamin E	18 (9.30%)	15 (26.80%)	35 (51.50%)
Dexamethasone	28 (14.50%)	8 (14.30%)	19 (27.90%)

and severe forms of ROP, as well as transition from the mild to severe form. Infants with the severe form of ROP were exposed to oxygen therapy on average three times longer than healthy infants.

IVH and/or PVL were found to be highly significant risk factors for the development of mild and especially severe form of ROP, but they did not affect the transition from mild to severe form. In the group of healthy infants 40.4% did not have CNS damage, while in groups with any form of ROP only 19.6% of infants did not have any CNS damage. IVH was most frequent in infants with some form of ROP (14.3%), while PVL was most frequent in infants with severe form of ROP (82.4%).

Sepsis was found to be a highly significant risk factor for the development of mild and severe forms of ROP and was especially uncorrelated to the transition from the mild to severe form of ROP. In infants with the severe form of ROP sepsis was found in 41.2% of cases.

The number of transfusions was also found to be a highly significant risk factor for the development of both types of ROP. The infants with the severe form of ROP received on average three times more transfusions than healthy infants.

Erythropoietin was found to be a highly significant factor of risk only for the development of severe forms of ROP. In this study, dexamethasone was not found to be a statistically significant risk factor, which indicates that the administration of dexamethasone potentially prevents the development of ROP. A hemodynamically significant PDA closed with Indomethacin was also not found to be a statistically significant risk factor for the development of ROP.

Administration of surfactant was found to be a highly significant risk factor for the development of ROP, especially for severe forms of ROP. Surfactant was administered to 45.6% of infants with severe form of ROP, 30.4% of infants with some form of ROP and 11.4% of infants which did not develop ROP.

Diuretics and Dopamine were found to be highly significant risk factors for the development of mild and especially severe forms of ROP. Diuretics were administered to 55.9% of infants with severe form of ROP and Dopamine to 38.2%.

Vitamin E was found to be a highly significant risk factor for the development of all forms of ROP and significant factor in transition from mild to severe form of ROP. Vitamin E received 51.5% of infants with severe form of ROP and only 9.3% of infants which did not develop ROP.

Out of six analyzed perinatal risk factors for development of some form of ROP, Caesarean section was found to be statistically significant ( $p=0.01$ ). None of these factors was found to have statistical significance for the development of the severe form of ROP.

Multivariate logistical regression analysis was done for all risk factors which were found to be statistically significant by the univariate regression analysis. This analysis found independent risk factors for the development of ROP and for transition from mild to severe form of ROP. BW and CNS damage were found to be independent risk factors for the development of any form of ROP (Table 3). BW and

**Table 2.** Group correlations for each of risk factors using univariate regression

Risk factors	p		
	A/B	A/C	B/C
Gender	0.248	0.952	0.359
Gestational age	0.000*	0.000*	0.002*
Birth weight	0.000*	0.000*	0.000*
Apgar score	0.037*	0.000*	0.119
Duration of mechanical ventilation	0.001*	0.000*	0.050*
Duration of oxygen therapy (days)	0.001*	0.000*	0.000*
Bronchopulmonary dysplasia	0.002*	0.000*	0.305
Central nervous system damage	0.001*	0.000*	0.218
Perinatal risk factors	0.013*	0.508	0.007*
Sepsis	0.033*	0.001*	0.410
Patent ductus arteriosus	0.083	0.017*	0.655
Number of blood transfusions	0.000*	0.000*	0.002*
Erythropoietin	0.012*	0.000*	0.197
Surfactant	0.001*	0.000*	0.084
Diuretics	0.001*	0.000*	0.015*
Dopamine	0.001*	0.000*	0.074
Vitamin E	0.001*	0.000*	0.005*
Dexamethasone	0.967	0.013*	0.068

\* statistically significant

**Table 3.** Independent risk factors for any form of retinopathy of prematurity

Risk factor	Sig.	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Birth weight	0.001*	0.998	0.997	0.999
CNS damage	0.010*	2.019	1.185	3.438

\* statistically significant; CNS – central nervous system

**Table 4.** Independent risk factors for transition from mild to severe form of retinopathy of prematurity

Risk factor	Sig.	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Birth weight	0.052*	0.998	0.996	1.000
Perinatal risk factors	0.002*	1.433	1.144	1.794

\* statistically significant

prenatal factors were identified as independent risk factors for transition from mild to severe form of ROP (Table 4).

## DISCUSSION

All factors that were found to be statistically significant using the univariate regression could have a direct impact on the development of ROP in addition to indicating the general condition of prematurely born and sick infants. ROP is a multifactorial disease, so univariate analysis is not a sufficient statistical method, which was also pointed out by other authors [4, 5, 25, 26]. While univariate analysis largely ignores the correlations of risk factors, multivariate logistical analysis reveals the mutual dependencies and is the method of choice for statistical analysis of risk factors in the development of ROP [26, 27]. Many authors, however, comment on the limitations of these multivariate methods [4, 13].

In our study, BW was found as an independent risk factor for the development of any form of ROP and tran-

sition from milder to severe form, as shown by the authors from the Institute of Neonatology, Belgrade [28]. Many studies have shown that low BW and GA are most frequent statistically significant risk factors for the development and progression of ROP [3, 5, 6, 7]. Our analysis did not find the GA to be an independent risk factor for the development of ROP. The possible cause is that our screening criteria included infants with higher GA and BW than those in the developed countries, where the severe form of ROP occurs in infants with BW less than 800 g and GA less than 26 weeks [27, 29]. The mean BW ( $1442.94 \pm 359.99$  g) and mean GA ( $30.10 \pm 2.74$ ) in the severe ROP population of our study group were comparable with those in infants in moderately and/or poorly developed countries. [7, 30-35]. The second possible reason is the larger percentage of infants with intrauterine growth retardation, which was not analyzed separately in this study.

Brain damage in preterm infants (IVH and PVL) was found as an independent risk factor for the development of ROP, confirming the findings of other authors [36, 37]. Hungerford et al [38] have found that 78% of infants with a severe form of ROP had a periventricular haemorrhage. Similar relationship was discovered by Procianny [39]. The majority of authors have pointed out a larger impact of IVH on the development of ROP (12), while our study found a larger percentage of infants with PVL. The frequency of PVL in all three groups was 62.14%, while the frequency of IVH was only 8.5%. Infants with a mild form of ROP more frequently had IVH, while infants with a severe form of ROP were found to have more frequent PVL. Other authors point out that the frequency of PVL is 4-26% in preterm infants in the neonatal intensive care unit (NICU) [40]. They point out that the incidence in autopsy studies is much larger and reaches 75%. Data on the frequency of PVL depend on the severity of the infant's condition when accepted in NICU, number of ultrasound examinations of CNS and the definition of PVL [41, 42, 43]. A large number of infants with PVL in our study is probably the consequence of early ultrasound CNS screening performed at our NICU, since in that way infants with transitional ischemic CNS developments were included in the study. The incidence of IVH ranges in literature from 20 to 60% [43, 44, 45]. Other authors have shown that IVH is more frequent in infants with a very small BW and severe form of ROP [12].

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Studies of ROP risk factor usually include well established risk factors: oxygen therapy, small BW and GA, large number of transfusions, sepsis, CNS damage etc. In addition to these well established factors, many studies also include other factors without well understood pathogenetic mechanisms; surfactant, erythropoietin, vitamin E, dopamine, diuretics, dexamethasone and others. Some studies also indicate the potential genetic predisposition for ROP. Lois Smith has determined that IGF-1 levels are deficient after premature birth, and that restoration of IGF-1 levels found in-utero may help prevent ROP [46]. In this study, we demonstrate that it is important to simultaneously consider all known risk factors, both peri- and postnatal. We would like to emphasize the impact of perinatal risk factors since this study shows their high statistical significance when analyzed together with postnatal factors. Univariate analysis was found the Caesarean section to be a statistically significant risk factor. Multivariate logistic regression showed that, in general, the existence of any pre-natal risk factor had impact on the development of severe form of ROP.

In our opinion, further studies of ROP risk factors should be directed toward establishing a common electronic database to include all known risk factors, both pre-natal and post-natal. By utilizing an individual case-by-case analysis and application of statistics and probability theory on a larger data-set would enable the development of properly calibrated weighted regression models that could capture complex interplays of many risk factors. This model would then enable the prediction of potential influence of post-natal risk factors based on the quantified impact of pre-natal risk factors.

## CONCLUSION

Our study found a high statistical significance for multiple known individual risk factors for the development of ROP. The most significant independent risk factors for the development of ROP were found to be BW and CNS damage. In addition to BW, prenatal risk factors were found as statistically significant independent risk factors for the development of severe form of ROP. According to our findings, in the analysis of the ROP risk factors it is important to simultaneously consider prenatal, perinatal and post-natal risk factors.

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## Анализа фактора ризика за развој ретинопатије код превремено рођене деце

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### КРАТАК САДРЖАЈ

**Увод** Ретинопатија прематуритета је мултифакторска болест која се најчешће јавља код веома мале и болесне превремено рођене деце и најзначајнији је узрок слепила код деце.

**Циљ рада** Циљ рада је био да се анализирају учесталост и фактори ризика који утичу на различите стадијуме ове болести.

**Методе рада** Студија је рађена у Центру за неонатологију Педијатријске клинике у Крагујевцу (Србија) од јуна 2006. до децембра 2008. године. Офталмолошким скринингом су обухваћена сва новорођена деца чија је телесна маса на рођењу била до 2.000 грама, односно деца гестационе старости до 36 недеља. Анализирано је осамнаест постнаталних и шест перинаталних фактора ризика у свим посматраним групама, као и однос између група за сваки фактор посебно.

**Резултати** Од 317 деце која су подвргнута офталмолошком скринингу, код 56 (17,7%) се развио почетни облик ретино-

патије, док је код 68 деце (21,5%) установљен тешки облик болести. Униваријантном анализом откривен је велики број статистички значајних фактора ризика за развој ретинопатије прематуритета, посебно за развој тешког облика болести. Мултиваријантном логистичком анализом издвојени су независни фактори ризика: мала телесна маса на рођењу ( $p=0,001$ ) и оштећења централног нервног система ( $p=0,01$ ). Независни фактори ризика за прелазак блажег у тежи облик ретинопатије били су: мала телесна маса на рођењу ( $p=0,05$ ) и перинатални фактори ( $p=0,02$ ).

**Закључак** Мала телесна маса на рођењу и оштећења централног нервног система били су фактори ризика за развој ретинопатије код превремено рођене деце. Перинатални фактори ризика означени су као значајни за погоршање обољења.

**Кључне речи:** ретинопатија прематуритета; фактори ризика; мултиваријантна статистичка анализа

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