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# THE ASSESSMENT OF RISK FACTORS FOR RETINOPATHY OF PREMATURITY

# PROCENA RIZIKO FAKTORA KOD RETINOPATIJE PREMATURITETA

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***Summary***

*Retinopathy of prematurity (ROP) is a potentially blinding eye disorder that primarily affects premature infants. Our study was conducted in order to determine which risk factors lead to the development of retinopathy of prematurity.*

*This retrospective study included 108 newborns with birth weight (BW) < 1500 g and gestation age (GA) < 33 weeks, over the period of two years, who were treated at the Clinic of Pediatric, University Hospital, Clinic Centre Banja Luka. In all preterm children, the impact of risk factors conditioned preterm birth (gestational age and birth weight), parameters of general health status (respiratory distress syndrome, apnea, perinatal asphyxia, frequent use of blood derivatives, sepsis, hyperbilirubinemia) and parameters of the treatment with oxygen therapy.*

*Out of 108 infants who fit the screening criteria, ROP was detected in 64 (59.2%) infants, 21(19.4%) of which had severe ROP requiring surgical intervention. Severe ROP was expressed in only 7.8% (5/64) of infants with GA > 30 weeks and in 12.5% (8/64) of infants with BW > 1250 g, compared to 25% (16/64) of infants with GA < 30 weeks and 20.3% (13/64) of infants with BW < 1250 g. The incidence of severe ROP was statistically significantly more frequent with progressively smaller birth weight BW < 1250 g (p <0.01) and the lower GA (gestational age) < 30 weeks (p <0.01). Using multiple logistic regression analysis for ROP, a long-term oxygen therapy (OR,15:54CI, 1.99-120.79) and a long duration of mechanical ventilation (OR,9.97; CI,3.06-32.51), there were obtained factors with a strong connection to the development of severe ROP. The following factors have a slightly lower correlation to the development of severe ROP: birth weight < 1250 g, gestation age < 30 weeks, respiratory distress syndrome, apnea, frequent use of blood derivatives and early sepsis.*

*Prematurity and low birth weight are significant risk factors for the development of ROP. Compromised pulmonary function with long-term oxygen therapy and frequent use of blood derivatives are important factors in the development of severe ROP.*

***Keywords:*** *retinopathy of prematurity, risk factors, preterm children*

***Sažetak***

*Retinopatija prematuriteta (ROP) je oboljenje oka koje može da vodi slepilu kod prevremeno rođene dece. Naša studija je sprovedena sa ciljem utvrđivanja koji faktori rizika dovode do razvoja retinopatije prematuriteta.*

*Retrospektivna studija obuhvata 108 novorođenčadi porođajne težine < 1500 g i gestacije starosti < 33 nedelje, lečenih tokom dvogodišnjeg perioda na Klinici za dječije bolesti, Univerzitetske bolnice Kliničkog centra Banja Luka. Kod sve prevremeno rođene dece je ispitivan uticaj faktora rizika uslovljenih prevremenim rođenjem (gestacijska starost i porođajna težina), parametrima opšteg zdravstvenog stanja (respiratorni distres sindrom, apnea, perinatalna asfiksija, politransfuzije, sepsa, hiperbilirubinemija) i parametrima lečenja sa oksigeno terapijom.*

*Od 108 novorođenčadi koji su imali kriterijume za praćenje, ROP je prisutan kod 64 (59.2%) novorođenčeta od kojih je 21 (19.4%) imalo teški ROP koji zahteva hiruršku intervenciju. Teški ROP se ispoljava kod samo 7.8% (5/64) novorođenčadi gestacijske starosti veće od 30 gestacijskih nedelje i kod 12.5% (8/64), PT > 1250 g u odnosu na 25% (16/64) koji su gestacijske starosti < 30 nedelja i 20.3% (13/64), PT < 1250 g. Učestalost pojave teškog ROP-a je statistički visoko značajna što je porođajna težina manja PT < 1250 g (p<0,01) i što je niža gestacija < 30 nedelja (p<0,01).*

*Koristeći multiplu logističku regresionu analizu dobili smo prediktivne faktore sa jakom povezanošću za pojavu teškog ROP-a, dugotrajnu oksigeno terapiju (OR, 15.54; CI, 1.99-120.79) i dugu primenu mehaničke ventilacije (OR, 9.97; CI, 3.06-32.51). Nešto nižu povezanost za razvoj teškog ROP-a imaju porođajna težina < 1250 g, gestacija starost < 30 nedelja, respiratorni distres sindrom, apnee, politransfuzije i rana sepsa.*

*Prematuritet i niska porođajna težina su veoma značajni faktori rizika za razvoj ROP-a., a kompromitovana plućna funkcija uz dugotrajnu oksigeno terapiju i politransfuzije su važni faktori u razvoju teškog ROP-a.*

***Ključne reči:*** *retinopatija prematuriteta, faktori rizika, prevremeno rođena deca*

## Introduction

Retinopathy of prematurity (ROP) is a disease that affects the retinal blood vessels during their development and it manifests itself by cessation of normal blood vessel development and by the occurrence of proliferative retinopathy. It occurs in several development phases and retrolental fibroplasia represents a completely destroyed visual function which is manifested by blindness.

Numerous risk factors which obstruct normal development of vascularization of the retina are responsible for the occurrence of retinopathy of prematurity. The most significant among them are: short gestation, low birth weight, long – term use of supplemental oxygen and many other factors which are mutually combined and complemented.

By improving neonatal care, survival rates are higher in children born too small for their gestational age and in children with low birth weight which increases the incidence of retinopathy of prematurity and leads to the development of more severe forms of diseases.[1, 2] The prevention of retinopathy of prematurity is focused on the elimination of risk factors and ophthalmologic screening.[3] Detecting and recognizing the early stages of this disease and timely and adequate treatment mean developing good visual function.

On the other hand, studies show that complex and expensive surgical procedures in treating severe stages of ROP followed by ablation and fibrovascular organization of vitreous body achieve good anatomical results. However, they are not accompanied by improved visual function. [4]

## Material and methods

### Patients

A two – year retrospective study was conducted in the Department of Pathological Neonatology with Prematurity and in the Department of Intensive Care of the Paediatric Clinic of the University Hospital Clinical Centre Banja Luka. The study included infants born in the Maternity Home of the Clinic of Gynaecology and Obstetrics of the University Hospital Clinical Centre Banja Luka and infants referred from regional centres in the Republic of Srpska. We conducted an analysis of 108 preterm infants on the basis of criteria for ROP screening programmes. Infants with severe congenital malformations and chromosome disorders and infants that had died before ophthalmological examination were excluded from the study. Examinees were divided into three groups: infants without ROP; infants with ROP, but with no need of surgical intervention; infants with "severe" disease that had to be treated with laser surgery.

### Methodology of ophthalmologic screening

Criteria of ophthalmologic screening for retinopathy of prematurity are accepted according to the protocols of the American Academy of Paediatrics.[5,6] The selection for screening included preterm infants born earlier than 33 weeks of gestational age and with birth weight below 1500 g, as well as infants that were at additional risk for ROP. Preterm infants at risk were selected for screening by paediatricians – neonatologists from the Department of Intensive Care. Maximum mydriasis was achieved by administration of Cyclopentolate 0.5%, eye drops and anaesthetic Novesine 0.4% was also instilled immediately prior to examination. The exam was made with the use of binocular indirect ophthalmoscope and 20 D magnifier. In order to examine peripheral areas of retina better, indentator was used [7]. During the screening process, the development of retinal blood vessels was monitored and preterm infants with ROP were selected.[8] By adhering to the criteria of the International Classification of Retinopathy of Prematurity– ICROP, data from each examination were entered into documentation on the localization of the endings of retinal blood vessels – (zone 1 – 3), expansion and stage 1 – 5.[9] Age when ROP was detected, maximum stage of ROP, localization and ROP treatment were determined.

### Identification of risk factors

Demographic data that were analysed included: gestational age in weeks, birth weight and sex. Clinical data included perinatal asphyxia, respiratory distress syndrome (RDS), apnoea, use of surfactant, pneumonia, persistent ductus arteriosus, sepsis, intraventricular haemorrhage, hyperbilirubinemia that required phototherapy.

With regard to the treatment, the oxygen was used in the form of controlled higher concentration of inspired oxygen (diffusion via atmosphere of the incubator or "hood"), by non – invasive positive – pressure ventilation and/or conventional mechanical ventilation. The condition of retinal blood vessel network was analysed with respect to the duration of the use of oxygen therapy and the form of respiratory support. All preterm infants treated with oxygen were continuously monitored by the use of pulse oximetry technique. Percutaneous value of hemoglobin oxygen saturation in arterial blood (SaO2) was measured.

Using the SPSS Statistics 20.0 software package, a statistical analysis was made. Methods of descriptive and analytical statistics were used in the analysis. In univariable comparison of risk factors between groups without ROP, infants with ROP that were not in need of a surgical treatment and ROP that required surgical treatment, Student's t – test and Chi – square test with an adequate significance level of $p<0.05$ were used. Predictive factors for the development of ROP were estimated by using multivariable logistic regression. Odds ratio was calculated and the 95% confidence interval for each risk factor was estimated.

Table 1. Anthropometric characteristics of preterm infants

| | Without ROP | With ROP that does not require surgery | Severe ROP |
|---|---|---|---|
| Gestational age, weeks | 31.6±1.3 | 30.8±1.4 | 28.8±1.5 |
| Birth weight, g | 1772.7±253.9 | 1469.6±282.2 | 1154.3±224.9 |
| Sex | | | |
| Male | 30 | 21 | 9 |
| Female | 14 | 22 | 12 |
| Total | 44 | 43 | 21 |

## Results

The paper presents results of the two – year retrospective study conducted with the aim of diagnosing retinopathy of prematurity and determining the risk factors that lead to the development of the disease.

Of the total number of infants (1186) treated in our departments, 9. 1 % of them (108) met the criteria to be monitored due to ROP. Sixty preterm infants were males and forty – eight were females. The incidence of severe ROP that required to be surgically treated was 21/108 (19.4%).

The first ophthalmologic screening examination was made in all infants starting from 31$^{st}$ week up to 37$^{th}$ week of gestation. The mean value was 34. 8±1.63 GW. ROP was present in 64 out of 108 (59.2%), out of which 21/108 (19.4%) had severe ROP that required to be surgically treated. No abnormalities were detected in 44 out of 108 (40. 7%).

The mean value of gestational age in all examined infants was 30.8±1.7 weeks (range 26 – 33), while the mean value of birth body weight was 1533.2±346.4 g (range 740 – 2370).

The mean value of birth body weight in infants with ROP that required to be surgically treated was 1154.3±224.9 g (range 740 – 1460) and gestational age was 28.8±1.5 weeks (range 26 – 31.4). Birth body weight in infants without ROP was 1772.7±597, 3g and gestational age was 31.6±1.3 weeks (Table 1).

Table 2 shows the characteristics of preterm infants without ROP and with ROP that do not require surgical intervention in comparison with infants with severe ROP that require surgical treatment, which was confirmed with ophthalmological screening examination. The incidence of severe ROP is significantly higher if birth weight is lower i.e. < 1250 g ($p<0.01$) and if gestation is shorter i.e. < 30 weeks ($p<0.01$). Prolonged oxygen therapy is highly statistically significant in infants that will develop severe ROP ($p=0.000$). Development of severe retinopathy of prematurity in comparison with the presence or absence of systemic diseases was also analysed and tested. The presence of a severe stage of ROP is statistically more frequent in a more severe stage of respiratory distress due to hyaline membrane disease, ($p<0.05$). The incidence of severe ROP is highly statistically significant if perinatal asphyxia, frequent apnoea, early sepsis are present (Table 2).

With the aim of demonstrating the significance of immaturity as risk factor, a multiple logistic regression model was designed. It includes all risk factors, i.e. gestational age, birth weight and various diseases such as respiratory distress syndrome, presence of apnoea, perinatal asphyxia, sepsis and hyperbilirubinemia. When it comes to most of the examined risk factors, there is a strong connection between severe ROP that requires surgery and exposure to the risk factors in infants with lower birth weight (OR 9.25; CI 3.20-26.69), shorter gestation (OR 10.06; CI 3.29-30.76), presence of apnoea (OR 14.24; CI 4.30-47.19), diseases such as respiratory distress syndrome (OR 3.76; CI 1.26-11.17), perinatal asphyxia (OR 6.50; CI 2.15-19.64), early sepsis and poly – transfusions (Table 3).

There is an exceptionally strong connection between severe ROP that requires to be surgically treated and exposure to oxygen therapy, especially when received for more than 10 days (OR 15.54; CI 1.99-120.79), and long – term mechanical ventilation (OR 9.97; CI 3.06-32.51). Pneumonia, late – onset sepsis, intraventricular haemorrhage, hyperbilirubinemia and presence of persistent ductus arteriosus are not statistically significant for manifestation of severe ROP.

## Discussion

In our study, higher ROP incidence is related to lower birth weight, shorter gestation, long – term oxygen therapy, mechanical ventilation, early sepsis, and blood poly – transfusions. Risk factors shown in literature vary because of the differences in methodology and in indications for the treatment of ROP [10].

During the two – year period of our activities, the general incidence of severe ROP was 1.8%. 21 out of 108 (19.4%) preterm infants had severe ROP requiring surgical intervention. Developing countries tend to demonstrate the presence of ROP requiring surgical intervention in

| Table 2. Relationship between retinopathy of prematurity and risk factors | | | |
|---|---|---|---|
| | **Without ROP and with ROP that does not require surgery** | **Severe ROP** | **p** |
| | | | |
| Gestational age, weeks | | | |
| GA<30 | 21 | 16 | <0.01 |
| GA>30 | 66 | 5 | |
| Birth weight | | | |
| BW<1250 g | 13 | 13 | <0.01 |
| BW>1250 g | 74 | 8 | |
| Perinatal asphyxia | | | |
| Yes | 9 | 9 | 0.001 |
| No | 78 | 12 | |
| RDS | | | |
| Yes | 40 | 16 | 0.013 |
| No | 47 | 5 | |
| Apnoea | | | |
| Yes | 20 | 17 | 0.000 |
| No | 67 | 4 | |
| Early sepsis | | | |
| Yes | 12 | 12 | <0.01 |
| No | 75 | 9 | |
| Hyperbilirubinemia | | | |
| Yes | 71 | 17 | >0.05 |
| No | 16 | 4 | |
| Oxygen therapy | | | |
| Yes | 79 | 21 | 0.000 |
| No | 8 | 0 | |
| Mechanical ventilation | | | |
| Yes | 26 | 17 | <0.05 |
| No | 61 | 4 | |

RDS – respiratory distress syndrome

infants born too large for their gestational age and infants born with greater birth weight, while the incidence is very diverse.[10, 11] Studies conducted worldwide indicate the differences in ROP incidence: Mathew and associates [12] from Scotland 4.8%, Pishava and associates [13] from Iran 9.5%, Yang and associates [14] from China 25%, Karna and associates [15] from the USA 7.8%, Ahmed and associates [16] from Bangladesh 4.4%, Wani and associates [17] from Kuwait 7.8%. The study of Hussain and associates [18] indicates a significant reduction in incidence and severity of ROP due to the application of surfactant. General incidence of ROP in infants was 21.3%, and the incidence of severe ROP was 4.6%.

In our study, screening was averagely performed in 54 infants within one – year period. The average birth weight was 1533.2 g, the mean gestational age was 34.8±1.63 weeks. In Goble's study the average gestational age of in-

Table 3. Multiple logistic regression analysis of risk factors related to the occurrence of ROP

| | OR | 95% CI | p |
|---|---|---|---|
| Gestational age, < 30 weeks | 10.06 | 3.29-30.76 | 0.000 |
| Birth weight < 1250 g | 9.25 | 3.20-26.69 | 0.000 |
| RDS | 3.76 | 1.26-11.17 | 0.013 |
| Surfactant | 6.50 | 2.15-19.64 | 0.000 |
| Apnoea | 14.24 | 4.30-47.19 | 0.000 |
| Pneumonia | 1.71 | 0.63-4.66 | 0.289 |
| Perinatal asphyxia | 6.50 | 2.15-19.64 | 0.000 |
| Early sepsis | 8.33 | 2.89-23.99 | 0.000 |
| Late sepsis | 0.35 | 0.09-1.29 | 0.104 |
| IVH | 2.73 | 0.60-12.49 | 0.180 |
| Poly-transfusions | 10.86 | 3.53-33.41 | 0.000 |
| Hyperbilirubinemia | 0.96 | 0.28-3.23 | 0.945 |
| PDA | 3.18 | 0.81-12.49 | 0.085 |
| Mechanical ventilation | 9.97 | 3.06-32.51 | 0.000 |
| Long-term oxygen therapy >10 days | 15.54 | 1.99-120.79 | 0.001 |

OR: Odds ratio; CI-95% confidence interval, RDS – respiratory distress syndrome, IVH – intraventricular haemorrhage PDA – persistent (patent) ductus arteriosus

fants who had undergone screening due to ROP was 29.1 weeks.[19]

In our study, shorter gestational age was established as a statistically highly significant risk factor ($p<0.01$) for the occurrence of ROP. The average gestational age among examinees was 30.8 ± 1.7 weeks and it ranged between 26 and 33 weeks. The incidence of ROP in infants with birth weight below 1250 g was 20.3% (13/64), whereas in infants with BW >1250 g, the incidence was 12.5%. All the studies stress preterm birth is a significant risk factor and that the incidence of ROP increases with immaturity. [20-23] Darlow and associates agree with such an interpretation and they state that children born before 25$^{th}$ gestational week are twenty times more likely to have severe form of ROP compared to children born after 28$^{th}$ gestational week.[24]

In our study, in the examined group of infants with the birth weight > 1460 g and gestational age > 31.4 weeks, there is no severe ROP, but there is a smaller number of infants with birth weight below 1000 g, which can be explained by a lower survival rate of children with low body weight, in our conditions. Similar results were obtained in other developing countries such as ours.[25-27]

As for the occurrence of ROP, Chen and associates have concluded that the exposure to oxygen is of greater importance for infants born at 23 – 25 weeks, while the infection is associated with ROP among infants born at 28 – 29 weeks.[19] In the study of Alpay and associates, the influence of numerous risk factors for development of ROP was explored. They emphasized apnoea, respiratory distress syndrome (RDS) and oxygen therapy as significant independent risk factors for the development of ROP.[28] In our study the presence of more severe respiratory distress due to hyaline membrane disease is significantly higher ($p<0.05$) in infants in whom ROP requires surgical treatment. Other author's studies also confirmed that respiratory distress syndrome affected the development of ROP.[21, 25, 29]

In our study, in infants who received long – term oxygen therapy, there was a significantly frequent occurrence of ROP that required to be surgically treated ($p<0.01$). Oxygen therapy was used for longer periods of time in children with low birth weight and shorter gestation and those children at the same time had more frequent occurrence of ROP requiring surgical treatment.

An optimal level of oxygen in the treatment of preterm infants is a constant quest. [22] It is being explored within a wide range of oxygen concentration. Control of oxygenation is achieved by elimination of the application of high oxygen concentrations. Lower concentrations will significantly reduce the incidence of severe ROP, as this was shown in the study of Wright and associates.[30] In most of the studies, the value of haemoglobin oxygen saturation

in preterm infants born before 32nd week ranged between 89% and 94%; in others between 85% and 95% or 83% and 93%. The application of controlled and limited saturation of haemoglobin with oxygen induced a decrease of the incidence of ROP requiring surgical intervention, [31, 32, 33] but there has been an increase in mortality. [34, 35]

In our study, the length of the application of mechanical ventilation was significantly more frequent ($p<0.05$) in the group of infants with ROP requiring surgical treatment than in infants who did not have ROP or who had ROP which did not require surgical treatment. Many authors emphasize that longer application of mechanical ventilation is associated with the development of severe forms of ROP.[21, 36-38] Finer and associates published the study in which they pointed out a lower incidence of severe ROP and chronic lung disease in children with very low birth weight during a restrictive application of mechanical ventilation by using non – invasive ventilation with positive pressure, in the nine – year period. [39] Mechanical ventilation is applied in preterm infants with severe forms of respiratory distress syndrome and they depend on a higher concentration of oxygen for achieving adequate saturation. During the application of mechanical ventilation, fluctuations of oxygenation are more frequent and a higher risk of hyperoxia is present. Key guidelines for reducing the incidence of ROP are avoiding hyperoxia early in the life of an infant, constant maintenance of a certain saturation of haemoglobin with oxygen and achieving a satisfactory growth rate.[40]

By using multiple logistic regression analysis, we found that a predictive factor with a strong relation to the occurrence of severe ROP was a longer exposure to oxygen therapy (OR, 15.54; CI, 1.99-120.79) and longer application of mechanical ventilation (OR, 9.97; CI, 3.06-32.51). The duration of oxygen therapy and higher oxygen concentration are directly related to the duration of mechanical ventilation. Immaturity and compromised lung function due to hyaline membrane disease are significant etiological factors for the development of ROP. Our results are consistent with the results which Shah and associates obtained.[21] Lower birth weight, shorter gestation, respiratory distress syndrome, the use of surfactant, presence of apnoic crisis, perinatal asphyxia, early sepsis and larger number of blood transfusions have a slightly lower correlation to the development of severe ROP.

Fortes Filho and associates [41] divided the children according to the gestation and monitored the impact of risk factors on the development of ROP. The conclusion was that those infants born before 32nd gestational week developed ROP due to the general immaturity and that infants born after 32nd week developed ROP because of being more ill. Preterm infants who developed ROP had some other severe associated diseases which may lead to disability, later in life.[42]

Numerous risk factors influence the development of ROP. Since this is a complex issue, it is necessary to work constantly on the exchange of experiences between different institutions and to acquire new information in order to improve prevention and to improve the disease outcome.

## Conclusion

By analysing the risk factors which affect the development of severe ROP in high – risk preterm infants, we have affirmed that significant predictive factors are immaturity, lower birth weight and shorter gestation with longer application of supplemental oxygen. Also, significant predictive risk factors include: the application of a larger number of blood transfusions, perinatal asphyxia, apnoea and early sepsis. Compromised pulmonary function due to respiratory distress syndrome which requires the application of a surfactant and a longer application of mechanical ventilation is associated and related with the development of severe ROP. Prevention of preterm birth, reasonable application of oxygen therapy and mechanical ventilation are necessary for reducing the incidence of retinopathy of prematurity. All of the above – mentioned can reduce the incidence and severity of ROP.

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