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Original Scientific Paper



# ASSESSMENT OF NEONATAL CARE STANDARD BY THE PREDICTIVE MODEL FOR RETINOPATHY OF PREMATURITY BASED ON WEIGHT GAIN

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SUMMARY – Care of extremely premature infants is in constant need for evaluation and progress. WINROP, a predictive model based on weight gain, has been developed to reduce the number of stressful examinations for retinopathy for prematurity. Validation studies of WINROP emphasize the difference of applicability in neonatal units of various practice. The aim of the study was to assess the standard of neonatal care by WINROP. Data on extremely premature infants were collected from medical records and entered in WINROP. High- and low-risk WINROP distribution and retinopathy of prematurity outcomes were analyzed. Fifty-four infants, gestational age ≤28 weeks, were included in the study after exclusion of weight related comorbidities. High risk was noted in 74% (n=40) of infants with 24% (n=13) developing retinopathy of prematurity requiring treatment. In low alarm group, there were 3 cases with severe disease. In conclusion, WINROP is not just a provider of predictive information on the severity of retinopathy of prematurity. High-risk alarm indicates the need of adjustment of nutritional strategies. Infants without pathological growth morbidities who develop severe retinopathy of prematurity in low-risk group point to other risk factors for retinopathy of prematurity to be evaluated and changed in future practice.

Key words: *Premature infant; Neonatal intensive care unit; Retinopathy of prematurity; Weight gain; Neonatal screening; WINROP*

## Introduction

The intrauterine milieu of the third trimester for an extremely premature infant is replaced by the extrauterine one for which it is not adequately prepared. The intrauterine milieu of the third trimester of an extremely premature infant is replaced by the extrauterine one for which it is not adequately prepared. Diagnostic, therapeutic, and other requisite interventions are performed in pursue for the well-being of the infant. These procedures are painful and stressful for an extremely premature infant with immediate and long-term consequences. It has been proven that repeated painful interventions can affect brain development with consequent neurological impairment. Painful procedures can lead to sleep and eating disorders. During painful interventional and diagnostic procedures, tachycardia, reduced oxygenation, and apnea may occur[1-6].

Retinopathy of prematurity (ROP) is a disease that affects only premature infants, but with progress

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in survival the share of this problem increases. Since blindness due to ROP can be prevented with timely treatment, screening for ROP is a mandatory part of care for premature infants. For this procedure, non-pharmacological methods and sweeteners, as well as local anesthetics have not been proven to be absolutely effective in preventing pain[7-14].

Poor weight gain is common in premature infants with multifactorial etiology primarily attributed to reduced intake and increased metabolism. The optimal growth rate has not been established and it seems that the growth rates achieved are still low[15-19]. Weight gain is related to insulin-like growth hormone-1 (IGF-1). IGF-1 affects the utilization of nutrients. IGF-1 values decrease after premature birth due to the loss of the mother's source and weak endogenous production. Postnatal hyperoxia and low IGF-1 levels interfere with VEGF-induced retinal vascular development with consequent retardation of retinal vessel growth. Hyperoxia had a significant impact in the history of ROP with extinction in developed countries. Many studies have shown that prolonged early IGF-1 deficiency and poor postnatal weight gain are associated with the severity of ROP, due to the significance and duration of vascular retardation. However, it is proven that nutrient intake is of limited effect on weight gain in early postnatal weeks[20-25]. Evidence that slow weight gain is a surrogate for low serum IGF-1 enabled creation of models based on early postnatal weight gain to predict severe types of ROP in order to reduce the rate of exposure to this stressful procedure. Some of the models are based on one-time evaluation and some are longitudinal[26-32].

The Weight, Insulin-like growth factor, Neonatal ROP (WINROP) is an online predictive model that records birth weight (BW) and gestational age (GA) of the infant and weekly weight measurements. It accumulates and calculates the risk of severe ROP requiring treatment. It alarms if an infant is at a high risk. WINROP aims to minimize the number of examinations in those at low risk and to closely monitor those infants at high risk of developing severe forms of ROP. WINROP has been validated in many developed and developing countries. Differences in results are thought to reflect differences in both perinatal and postnatal care[32-34].

The possible inapplicability of WINROP and other models in countries with evolving neonatal care is particularly emphasized due to the possible influence of other risk factors, as well as minor limitations of oxygen therapy. The hypothesis is that many of the postnatal risk factors described, such as anemia, sepsis, transfusion and others, act through a common pathway by lowering the value of IGF-1, and that their influence can be captured by simply considering weight gain. Oxygen therapy is an important exception, especially in developing countries. In countries where children with higher GA and BW develop severe forms of ROP, the possibility of other pathophysiological mechanisms unrelated to low IGF-1 values is noted. High oxygen supplementation, as well as the complexity of respiratory and nutritional measures in the retrospective model may also play a role. Existing models in high- and low-income countries are validated with different applicability results[35-37].

The standard of neonatal care is usually assessed by outcomes, morbidity and mortality, and references to the practices applied. Evaluation of care for individual infant is assessed by the ongoing changes and the condition of the infant. Sufficiency of growth is often judged by adopted growth charts.

The aim of this study was to assess the standard of neonatal care by the results of WINROP.

## Methods

Infants of GA ≥24 and ≤28 weeks and BW ≤1250 grams born in our institution during a 7-year period (2013-2019) were planned for the study. Infants with conditions that can significantly affect weight gain, such as hydrocephalus, hydrops, anasarca, long-term oliguria and polyuria (>20 days), intestinal perforation (severe forms of necrotizing enterocolitis) were to be excluded from the study, as well as infants with intrauterine growth retardation and major malformations. Duration of mechanical ventilation (invasive and noninvasive), duration of oxygen therapy, and duration of parenteral nutrition were recorded. Number of transfusions (packed red cells) *per* individual infant was recorded. Data were extracted from medical records.

Screening for ROP was initiated at postmenstrual age of 31 weeks or at 4 weeks of chronological age depending on GA and repeated every 1-2 weeks as recommended. ROP was classified by the International Classification of Retinopathy of Prematurity (ICROP)[38] and categorized according to the Early Treatment of ROP (ETROP) into ROP type 1, aggressive posterior ROP (APROP), ROP type 2,

mild forms of ROP as non-type ROP, and no ROP. Treatments were conducted according to ETROP[39]. Screening, diagnosis and treatment were performed by ophthalmological experts. ROP outcomes were recorded for every infant.

Data on GA, BW and weekly weight measurements were entered in WINROP. The alarms of high risk were recorded for every infant. Distribution of low- and high-risk designations with ROP outcomes was analyzed.

Analyses were performed by use of MedCalc® Statistical Software version 20.116 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022). Quantitative variables were expressed as medians, and categorical variables as numbers and percentages. Fisher-Freeman-Halton test was used for differences between categorical variables. Sensitivity, specificity, positive predictive value and negative predictive value were calculated according to WINROP results and ROP outcomes. The 95% confidence intervals (CI) were calculated. A value of $p<0.05$ was considered statistically significant.

Ethical approval was obtained for the broader study from the institutional Ethics Committee. Parental consent was not required as infants were anonymized and data extracted as part of routine care of extremely premature infants.

## Results

After strict exclusion criteria and due to the lack of data on a number of infants, 54 infants were included in the study. Median GA of the infants was 27 weeks and median BW was 895 grams (Table 1). Median duration of mechanical ventilation and oxygen therapy was 31.5 and 60 days, respectively. Median parenteral nutrition was 22.5 days. Median number of red blood cell transfusions was 3 (Table 1).

Thirteen (24%) infants developed severe ROP that required treatment (ROP type 1 and APROP). Two

*Table 1. Birth and treatment characteristics*

| | N | Min | Max | Median |
|---|---|---|---|---|
| Gestational age (weeks) | 54 | 24 | 28 | 27.00 |
| Birth weight (grams) | 54 | 615 | 1240 | 900.00 |
| Mechanical ventilation (days) | 54 | 11 | 73 | 31.40 |
| Oxygen therapy (days) | 54 | 21 | 106 | 60.00 |
| Parenteral nutrition (days) | 54 | 10 | 54 | 22.50 |
| Transfusion (number) | 54 | 0 | 8 | 3.00 |

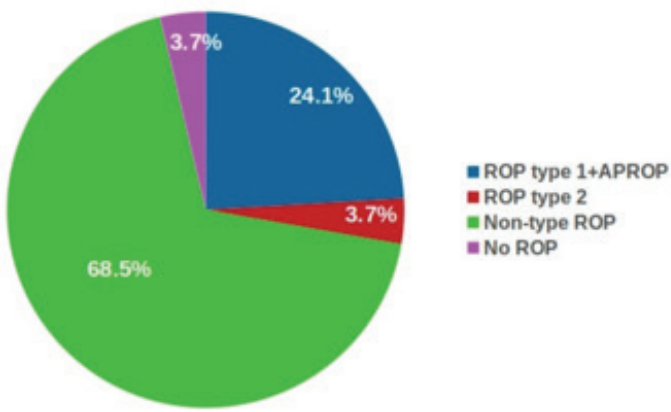


*Fig. 1. Distribution of ROP outcomes in study population.*

ROP = retinopathy of prematurity; APROP = aggressive posterior ROP

*Table 2. Difference in distribution of ROP types according to gestational age in infants who developed ROP*

| ROP types | Gestational age (weeks) | | p value |
|---|---|---|---|
| | ≤26 | 27-28 | |
| ROP type 1 + APROP | 42.9% | 12.9% | 0.034 |
| ROP not requiring treatment | 57.1% | 87.1% | |

ROP = retinopathy of prematurity; APROP = aggressive posterior ROP

*Table 3. Timing of high-risk alarm according to infant chronologic age and postmenstrual age*

| High-risk alarm | N | Min | Max | Median |
|---|---|---|---|---|
| Chronologic age (weeks) | 54 | 0 | 10 | 3.00 |
| Postmenstrual age (weeks) | 54 | 27 | 34 | 30.00 |

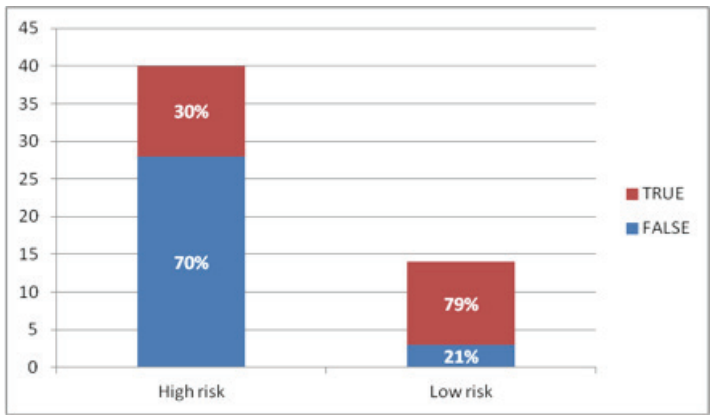


*Fig. 2. Distribution of false and true results in high-risk and low-risk groups: number (y axis) and percentage of infants per group.*

*Table 4. Sensitivity and specificity of WINROP to identify severe ROP*

| Severe ROP (n) | | No severe ROP No ROP (n) | | % (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| High risk | Low risk | High risk | Low risk | **Sensitivity** | **Specificity** | Positive predictive value | Negative predictive value |
| 12 | 3 | 28 | 11 | **80.0%** (51.9-95.7) | **28.2%** (15.0-44.8) | 30.0% (23.7-37.1) | 78.6% (26.2-56.8) |

ROP = retinopathy of prematurity; CI = confidence interval

(3.7%) infants developed ROP type 2 with no further progression. Only two (3.7%) infants did not develop any form of ROP. The rest of infants developed milder forms of ROP (non-type ROP) (Fig. 1).

Distribution of ROP requiring treatment yielded significant difference between the infants of GA 24-26 weeks *versus* those of GA 27-28 weeks (Table 2).

Median postmenstrual age of WINROP alarm was 30 weeks and of chronological age 3 weeks (Table 3). High alarm was turned on for 40 (74%) infants. There were 3 cases of severe ROP requiring treatment in the low-risk group (Fig. 2, Table 4).

## Discussion

Many studies that validated WINROP in their neonatal units have reported reduction of examinations. The prevalence of high-risk alarms and the number of false-positive indications for screening refer to unsatisfactory postnatal growth achieved in the population of infants of GA ≤28 weeks in our unit. It especially refers to the very early postnatal course of high-risk alarm with a 3-week median of chronological age. Most studies report on alarms at a median of 2 or 3 weeks after birth, range 0-9 weeks. With our study, 20% less infants would be examined solely with indications by WINROP. In individual analysis, delay in the initiation of screening was noted. Six infants would be spared of one examination each.

Three infants who developed ROP requiring treatment were evaluated as of low risk. One of those infants had intraventricular hemorrhage grade 3 with temporary ventricular dilatation that resolved but might have transitionally influenced weight measurements without meeting exclusion criteria, as speculated in another validation study[34]. However, it also refers to other factors apart from weight gain to dominate in the pathophysiology of ROP in infants evaluated by this study. As many studies validated WINROP in their neonatal units, the reported sensitivity ranges from 64.7% to 100% and specificity from 23.9% to 89.0%[34,40-49]. In our study, the sensitivity was 80.0% and specificity only 28.2% (Table 4). Still, our study was conducted with infants of GA ≤28 weeks and others, as WINROP formulates, of GA up to 31+6 weeks. As reported in other studies, most infants with severe ROP missed by WINROP alarm were of GA <28 weeks. Considering GA, one study reports 19% specificity in the group of GA <28 weeks[49]. The low specificity in our study could be attributed to the low gestational age of the infants and their poor growth.

The more immature the infant, the harder it is to achieve adequate growth. The problem encountered by neonatologists all over the world is reflected in the high number of false positives reported in WINROP validation studies[16-19,34,50-54]. Some suggest it may be due to difference in the expected growth of their population[46]. Poor postnatal growth disturbs neurodevelopment, as well as development of other organs[15]. Since optimal growth of extremely preterm infants in terms of optimal outcome remains to be defined, striving to achieve growth according to WINROP would not only reduce severe ROP, but also other complications of prematurity[55].

There was a high incidence of severe ROP in the study population. Due to rigid exclusion criteria of infants with complicated course, the incidence in our unit might be even higher. The incidence of ROP in this GA and BW is still considered high. Most countries have an inclusion criterion of GA ≤28 weeks, and many GA ≤32 weeks. In underdeveloped and developing countries, the screening limits are higher. In highly developed countries, the gestational age limit for screening is lowered as the occurrence of ROP is limited to extremely immature babies with quality care[56-66]. In another weight gain based model G-ROP (Postnatal Growth and Retinopathy of Prematurity Study), GA of ≤28 weeks is an absolute inclusion criterion[26]. In our study, there were significantly more infants with ROP requiring treatment in the group of GA 24-26 weeks compared to the group of GA 27-28 weeks, as expected (Table 2).

The study that included infants from our and another neonatal unit adapted the criteria proposed adapted in the Co-ROP model (Colorado ROP)[31,67]. The study presented adjustment of weight gain at chronologic age of 4 weeks as an inclusion criterion for screening. The Co-ROP set the cut-off weight gain ≤650 grams and this study set it at ≤932 grams for the population addressed. Their study revealed an insufficient growth of infants in these neonatal units, reflecting the standard of care as well. The national guidelines for the screening program in Croatia recommend the inclusion criteria of GA ≤32 weeks and/or BW ≤1500 grams. Exceptionally, infants of GA >32 weeks and/or BW up to 2000 grams are included depending on the complexity of their course evaluated by a neonatologist. The study justified default inclusion criteria.

This assessment is an indication of presumptive insufficiency of care and need of improvement in our unit. In a retrospective study, the potential changes in neonatal care may reduce the generalizability of the criteria. The limitation of the study was a small number of infants in a recent period as we are witnessing changes in practice. This especially addresses an extensive period of oxygen therapy revealed in the analysis, which is a dominant risk for ROP. There are other aspects of treatment, care and outcomes that need to be analyzed in pursue of progress.

Considering individual infant, high-risk alarm by WINROP indicates the need of adjustment of nutritional strategies, while infant designated as low

risk who develops severe ROP should be followed up with special attention to other complications and chronicities of prematurity.

## Conclusion

To our knowledge, this is the first Croatian study using WINROP. Our aim was not to validate the WINROP predictive algorithm since the study included a limited number of infants with extremely low GA and the time period involved. WINROP is recommended as a guide for neonatologists to closely monitor infants at high risk of developing severe ROP and reduce the number of examinations in those at low risk. In our study, we demonstrated it not only to be a valuable tool for monitoring the risk of ROP but also for assessing growth and nutritional measures, as well as the general standard of neonatal care in continuous efforts for improvement.

Although our analysis did not show major reduction of ophthalmologic examinations, as the priority is to avoid blindness in even one child, any reduction of exposure to procedural stress in an individual infant should count as well.

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Sažetak

## PROCJENA STANDARDA NOVOROĐENAČKE SKRBI PREDIKTIVNIM MODELOM ZA RETINOPATIJU NEDONOŠČADI TEMELJENIM NA PRIRASTU TJELESNE MASE

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Skrb o izrazito nezreloj nedonoščadi zahtijeva stalnu procjenu i napredak. Prediktivni model temeljen na prirastu tjelesne mase WINROP razvijen je u svrhu smanjenja stresnih pregleda u probiru za retinopatiju nedonoščadi. Validacijske studije WINROP-a naglašavaju razliku u primjenjivosti u neonatalnim jedinicama različitih standarda. Cilj studije bio je procijeniti standard neonatalne skrbi upotrebom WINROP-a. Podatci o ekstremno nezreloj nedonoščadi prikupljeni su iz medicinske dokumentacije i uneseni u WINROP. Analizirana je podjela visokog i niskog rizika prema WINROP-u i ishoda retinopatije nedonoščadi. U studiju je bilo uključeno 54 nedonoščadi gestacijske dobi ≤28 tjedana nakon isključenja supostojećih bolesti povezanih s tjelesnom masom. Visoki alarm zabilježen je u 74% (n=40) djece, a 24% (n=13) razvilo je retinopatiju nedonoščadi koja je zahtijevala liječenje. U skupini niskog alarma zabilježena su 3 slučaja s teškom bolešću. Dakle, WINROP ne pruža samo prediktivnu informaciju za ozbiljnost retinopatije nedonoščadi. Alarm visokog rizika ukazuje na potrebu prilagodbe prehrambenih strategija. Nedonoščad bez patoloških poremećaja rasta koja su razvila ozbiljnu retinopatiju nedonoščadi u skupini niskog rizika upućuje na druge čimbenike rizika za retinopatiju nedonoščadi za procjenu i promjenu u budućoj praksi.

Ključne riječi: *Nedonoščad; Jedinica intenzivnog liječenja novorođenčadi; Retinopatija nedonoščadi; Prirast tjelesne mase; Novorođenački probir; WINROP*