**Algorithm for predicting threshold retinopathy of prematurity is
insufficient and fundus examinations are still needed up to 31
weeks**

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Short title: Algorithm for predicting retinopathy of prematurity

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Abstract

Aim: We evaluated the weight, insulin-like growth factor-1, neonatal, retinopathy of prematurity (WINROP) algorithm for very premature infants.

Method: Infants born before 32 weeks who had undergone fundus examinations in the neonatal intensive care unit at the University Hospital of Nancy were included in this French retrospective cohort study from July 2012 to July 2016. We evaluated how well the WINROP software predicted threshold retinopathy of prematurity (ROP).

Results: We studied 570 infants with a mean gestational age of 28.7 ± 1.8 weeks and a mean birth weight of $1,110 \pm 297$ grams: 28.1% had ROP and 1.2% had threshold ROP. The overall WINROP sensitivity was 57.1%, specificity was 46.0%, predictive positive value was 1.3% and predictive negative value was 98.9%. At more than 30 weeks of gestation or 1,250 grams, these figures rose to a respective specificity of 100% and 95.7% and respective predictive negative value of 100% and 100%. There were independent associations between the severity of ROP and the Apgar Score at five minutes, the duration of oxygen therapy and non-invasive ventilation.

Conclusion: WINROP performed better on preterm infants born after 30 weeks or over 1,250g. Fundus examinations remain necessary for those born before 31 weeks or under 1,251g.

Key Notes

- We evaluated the weight, insulin-like growth factor-1, neonatal, retinopathy of prematurity (WINROP) algorithm for very premature infants.
- Our study of 570 infants born before 32 weeks showed that WINROP was better at predicting risk of threshold retinopathy of prematurity of preterm infants born after 30 weeks or weighing over 1,250g.
- It is still necessary to carry out fundus examinations of preterm infants born before 31 weeks or weighing under 1,251g.

Keywords Algorithm, Fundus examination, Premature infants, Retinopathy of prematurity, Screening

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the main causes of avoidable visual impairment in children (1). The unmodifiable risk factors initially described by the Australian and New Zealand Neonatal Network, back in 2005, were a birth weight at 1,500 grams or less and a gestational age of less than 33 weeks of gestation. They also noted that severity increased with increasing prematurity (2). The main modifiable risk factor that has been identified is oxygen (3,4). Low serum insulin-like growth factor-1 concentration has also been shown to play an important role (3,5). Other described risk factors have included ethnicity (3,6) intra uterine growth restriction (2,3,7), hyperglycaemia (3,8-10), formula feeding, the lack of omega-3 long-chain polyunsaturated fatty acids in the diet (3,4,11), infections (3,4,10) and red blood cell transfusions (3,4,10). Associated comorbidities that have been described are bronchopulmonary dysplasia, necrotising enterocolitis and intraventricular haemorrhage (3).

A prognostic classification was developed by the authors of the Early Treatment for Retinopathy of Prematurity study and this defined two types of severe ROP. These were threshold ROP that required treatment and pre-threshold ROP that risked becoming threshold ROP and required screening twice a week (12).

One study reported that less than 2% of children screened for ROP required treatment (13). The diagnostic performance was therefore low. On the other hand, the number of fundus examinations has been estimated to be 5.4 per infant (14). Fundus examinations are stressful for premature infants (15), so it is important to optimise screening.

The French Ophthalmology Society has produced new French guidelines in 2016 for screening ROP that have not yet been published. These recommend screening

infants born before 31 weeks of gestation or with a birth weight below 1,251 grams at birth for ROP. They also state that infants with a birth weight between 1,251 and 2,000 grams should be screened if the infant presents with risk factors such as sepsis or has received prolonged oxygen therapy or prolonged vasopressor therapy.

Several algorithms for screening have been developed, including the free weight, insulin-like growth factor-1, neonatal, retinopathy of prematurity (WINROP) algorithm (16), which was developed by the The Sahlgrenska Center for Pediatric Ophthalmology Research at the University of Gothenburg, Sweden. WINROP was developed for infants born below 32 weeks of gestation and its aim was to predict the individual risk of threshold ROP by taking into account the infant's postnatal evolution (17,18). It is based on weight and the blood levels of insulin-like growth factor-1. The latter are correlated with fetal and postnatal growth, making the assessment of weight gain sufficient when using WINROP (5,19,20). WINROP is an inexpensive, simple, routine, fast, reproducible test that is carried out on a daily basis.

The aim of this study was to evaluate the performance of the WINROP algorithm with regard to predicting threshold ROP in very premature infants.

PATIENTS AND METHODS

This retrospective cohort study comprised infants born below 32 weeks of gestation and hospitalised in the neonatal intensive care unit at the University Hospital of Nancy, France, from July 2012 to July 2016. They were included if their medical records included the results from a fundus examination for ROP carried out with the ophthalmic imaging system Retcam (Clarity Medical Systems, California, USA). Infants with other ophthalmological pathologies, genetic diseases, hydrocephalus and those who died before 40 weeks of gestation were excluded.

During the study period our unit screened all premature infants born at up to 32 weeks of gestation or with a birth weight of up to 1,500 grams. The first examination took place at four weeks of actual age for infants born from 27 weeks of gestation and at an adjusted age of 31 weeks of gestation for infants born earlier. After that fundus examinations were carried out in accordance with international recommendations (2).

The haemoglobin oxygen saturation targets were 88-95% during this period. Infants were followed until 40 postmenstrual weeks and their weight was recorded on a weekly basis. We evaluated how effectively the WINROP algorithm was at predicting threshold retinopathy in the entire cohort, with regard to sensitivity, specificity, positive and negative predictive values. The gold standard was the clinical diagnosis according to good practice recommendations. We also specifically evaluated the performance of WINROP on the infants excluded by the new French guidelines, namely infants born at 31 or more weeks of gestation or with a birth weight of 1,251g or more.

Perinatal drugs and environmental data were collected from the infants' files and were evaluated by a descriptive analysis with means, standard deviations, medians based on first and third quartiles and percentages. These data were analysed with regard to severe ROP, which was defined by threshold and pre-threshold ROP. The quantitative variables were compared by the Student's t parametric test, while the qualitative variables were compared by using the chi-square test after verification of the application conditions. In the case of non-Gaussian populations, the Mann and Whitney, Kruskal Wallis and chi-square tests were used. Risk factors for any ROP with a p value of <0.1 in the bivariate analysis were then included in a stepwise multiple linear regression model with tolerance set at 10^{-5} , the probability to remove

set at 0.15 and 95% confidence intervals. The threshold for statistical significance was set at $p < 0.05$.

Parents were informed of this study by a specific newsletter and provided written consent. This research was performed in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (number: NCT03347799).

RESULTS

We enrolled 570 infants and the recruitment process is detailed in Figure 1. The mean gestational age and birth weight were 28.7 ± 1.8 weeks of gestation and $1,110 \pm 297$ grams. The characteristics of our study population and the associations between ROP and perinatal factors in the bivariate analysis are reported in Table 1.

The average number of fundus examination per infant was 2.9 ± 2.2 and we found that 28% of the infants had various stages of ROP. Threshold ROP was found in 1.2% of the infants and pre-threshold ROP was found in 5.3%. The mean corrected age at the most severe stage of ROP was 37 ± 3 weeks of gestation for threshold ROP, 34 ± 2 weeks of gestation for pre-threshold ROP and 35 ± 3 weeks of gestation for other ROP. The high-risk alarm for the WINROP algorithm was triggered in 54% of cases. Those alarms were not associated with sex, multiple pregnancy, antenatal corticosteroid, intraventricular haemorrhage and early-onset sepsis. However they were significantly associated ($p < 0.05$) with the following: a lower gestational age (100%, 100%, 98.0%, 92.9%, 80.9%, 74.0%, 11.0% and 0% at respectively 24, 25, 26, 27, 28, 29, 30 and 31 weeks of gestation), intrauterine growth restriction (100% versus 45.9%), bronchopulmonary dysplasia (63.9% versus 36.7%), postnatal corticosteroid (79.1% versus 20.9%), red blood cells transfusion (73.1% versus 26.9%), medical treatment of patent ductus arteriosus (70.3% versus 29.7%),

surgical treatment of patent ductus arteriosus (73.7% versus 26.3%), late-onset sepsis (68.2% versus 31.8%), blood inflammation (66.0% versus 34.0%), necrotising enterocolitis (71.3% versus 28.8%), hyperglycaemia (86.1% versus 13.9%) and insulin therapy (86.7% versus 13.3%).

The delay between birth and the trigger was 13 ± 1 days. The delay between the trigger and the discovery of all stages of ROP was 33 ± 20 days and it was 41 ± 24 days for the most severe stage of ROP. The delay between the trigger and the treatment of ROP, when necessary, was 64 ± 52 days.

The WINROP trigger was associated with threshold ROP in four out of 308 alarms and threshold ROP was present in three out of 262 infants without alarms. Thus, the WINROP sensitivity was 57.1%, the specificity was 46.0%, the predictive positive value was 1.3% and the predictive negative value was 98.9%. No threshold ROP was found for infants born at 31 weeks of gestation or more or weighing 1,251 grams or more and the specificity was 100% and 95.7%, respectively, and the predictive negative values were both 100%.

Severe ROP was associated with a lower gestational age and a lower birth weight than no severe ROP or no ROP and the figures were 26.6 ± 1.4 versus 28.8 ± 1.7 weeks of gestation ($p < 0.001$) and 831 ± 162 versus $1,166 \pm 292$ grams ($p < 0.001$). The factors associated with severe ROP are presented in Table 1. We did not show any overall relationship between infants with intrauterine growth restriction and severe ROP. However, the number of infants with an intrauterine growth restriction differed between infants with a gestational age of below 28 weeks and the group of infants from 28 weeks of gestation (43.3% versus 8.4% respectively). When we considered gestational age as a confounding factor, there was a significant relationship between infants with intrauterine growth restriction and severe ROP

($r=0.291$, $p=0.037$). Severe ROP was not associated with necrotising enterocolitis, except in most severe forms of stages IIb, IIIa and IIIb, when they were 16.7% versus 9.5%, 16.7% versus 1.4% and 16.7% versus 4.1%, respectively ($p=0.047$). Multivariate stepwise linear regression showed an independent association between the severity of ROP and low birth weight, a low Apgar Score at five minutes, a longer duration of oxygen therapy, a longer duration of postnatal corticosteroids and the duration of non-invasive ventilation ($r=0.569$, $p<0.001$).

Oxygen therapy duration was delivered for a mean of 32 ± 25 days in infants without ROP versus 65 ± 28 days in infants with any ROP ($p<0.001$) versus 83 ± 23 days in infants with severe ROP ($p<0.001$).

DISCUSSION

The incidence of threshold ROP in our cohort agreed with the literature (13). The point at which high-risk alarms were triggered, the time between alarm triggers and treatment and the performance of WINROP were consistent with several studies (21–23). Unlike the initial validation papers (16,22), our study showed that WINROP was not perfect for screening threshold ROP and these findings agreed with a paper published in 2018 (24). Thus, with regard to the limits of gestational age and birth weight in the new but unpublished French guidelines on screening, we confirm that fundus examination remains necessary for infants born before 31 weeks of gestation or with birth weight of up to 1,250 grams. Nevertheless, the absence of WINROP triggering may allow waiving fundus examination for infants born at 31 weeks of gestation onwards or with birth weight of 1,251g or more. However, WINROP can only be used to screen the infants born before 32 weeks of gestation (22). This leaves a grey area for infants born from 32 weeks of gestation onward who have a birth weight of between 1,251 and 2,000 grams.

The use of the WINROP algorithm is based upon gestational age, birth weight and weekly weight measurements (22,25). In our study the high-risk WINROP alarm was associated with intra uterine growth restriction, which was not associated with severe ROP. However, WINROP was associated with all situations linked to bad anabolism, because it is based on weight gain, which is impaired in these situations. This suggests that the impact of birth weight may be given too much emphasis in the algorithm, which is based on a standard weight range for gestational age. It appears that postnatal weight gain may be more important than birth weight. For example, Jung et al showed that infants born before 28 weeks of gestation, with a birth weight that was over the 70th percentile, were not identified by WINROP as having a high risk of developing severe ROP (23).

WINROP could be improved by considering additional parameters, including those identified by our multivariate analysis. For example, the Apgar score at five minutes, any use of oxygen therapy and any use of post-natal corticosteroids could easily be added to the algorithm.

WINROP is free, it is simple to use with an online monitoring system and it can be used on just weekly weight gain measurements (22,25). So, even if WINROP is not supposed to be used on its own for screening ROP, it can help to target high-risk infants in centres that do not have easy access to ophthalmic screening.

Otherwise, the goal of this algorithm should be, at the very least, to limit the number of eye fundus examinations that are carried out. It would be interesting to evaluate the result of using WINROP and just one fundus examination. We propose that this examination could be carried out at 32 weeks of gestation as this is the mean age at the most serious stage of ROP.

According to the literature a number of factors seem to be associated with severe ROP, such as multiple pregnancies, red blood cell transfusions, sepsis, hyperglycaemia, intraventricular haemorrhage, bronchopulmonary dysplasia and patent ductus arteriosus (3,4,8–10,12). In addition, severe ROP has been associated with severe enterocolitis, from stage IIb to IIIb (3). This could be explained by common factors like associated inflammation and poor weight gain. When we considered gestational age as a confounding factor, we also found a significant relationship between infants with intrauterine growth restrictions and severe ROP. This finding was consistent with the literature (2,3,7,26).

In our bivariate analysis, inflammation and sepsis were associated with severe ROP. Postnatal inflammation has been reported to increase severe ROP, with abnormal retinal vascular development and vessel anastomosis (27). Our study showed that late-onset sepsis, but not early-onset sepsis, was associated with severe ROP. So, the timing of the inflammation seems to play an important role in the development of severe ROP. Beaudry-Richard et al argued that early onset sepsis may be overshadowed by early inflammation, which is a major cause of preterm delivery especially for very preterm infants. As a result, early inflammation should be regarded as a main risk factor for ROP. However, the mechanism of early inflammation that triggers detrimental effects in the retina during ROP is still unclear and difficult to be evaluated and predicted (28).

In accordance with the literature (3,8-10), hyperglycaemia was also associated with severe ROP in our study. One study has suggested that these two factors are potentially linked by the inhibition of angiogenesis, which induces inflammation and neuronal degeneration in the retina (8).

The use of postnatal corticosteroids was associated with severe ROP in our study and this has previously been reported in the literature (29). Given the importance of inflammation in the pathophysiological mechanism of ROP, it would be interesting to investigate whether corticosteroids are a real risk factor for severe ROP or whether inflammation appears as a confounding factor in this relationship.

Likewise, hyperglycaemia (3,8-10) and the use of insulin were associated with severe ROP in our cohort and in the literature. However, a detailed study is required to understand the physiopathological mechanism of their relative role with regard to ROP. Some studies have suggested insulin, rather than hyperglycaemia, as a risk factor (30), but others have stated that insulin is a protective factor for severe ROP in patients with hyperglycaemia (8,9).

The strengths of our study were that our hospital records contained detailed eye fundus images and we were able to study a large population over a number of years. The main limitation was the retrospective nature of our study.

CONCLUSION

Using the WINROP algorithm at 31 weeks of gestation onwards or with birth weight of 1,251g or more, on our cohort of preterm infants, provided a respective specificity of 100% and 95.7% and respective predictive negative value of 100% and 100%.

However, fundus examinations remain necessary for those born before 31 weeks of gestation or weighing under 1,251g.

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ABBREVIATIONS

ROP, Retinopathy of prematurity; WINROP, weight, insulin-like growth factor-1, neonatal retinopathy of prematurity.

CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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Table 1: Factors associated with severe ROP

Perinatal factors	% (n=570)	No ROP / other ROP	Severe ROP (n=37)	p values
Sex, male	52.5%	53.5 %	37.8%	0.088
Gestational age < 31 weeks of gestation	82.6%	81.4%	100%	0.004
Intrauterine growth restriction	15.3%	15.2%	16.2%	0.871
Multiple pregnancy	30.7%	29.5%	48.6%	0.025
Antenatal corticosteroid	86.8%	87.7%	83.8%	0.717
Postnatal corticosteroid	22.6%	18.6%	81.1%	<0.001
Intraventricular haemorrhage	25.6%	24.6%	40.5%	0.031
Red blood cells transfusion	49.0%	45.5%	100%	<0.001
Bronchopulmonary dysplasia (oxygen > 28 days)	63.2%	61.1%	91.9%	<0.001
Use of vasopressor therapy	19.7%	16.7%	62.2%	<0.001
Medical treatment of PDA	24.2%	21.0%	70.3%	<0.001
Surgical treatment of PDA	10.0%	7.1%	51.4%	<0.001
Early-onset sepsis	10.5%	10.3%	13.5%	0.576
Late-onset sepsis	50.1%	46.8%	97.3%	<0.001
Blood inflammation (CRP > 30 mg/l)	46.2%	44.2%	75.0%	<0.001
Necrotising enterocolitis	14.2%	14.0%	16.2%	0.710
Hyperglycaemia (>11 mmol/l)	20.2%	17.3%	63.9%	<0.001
Insulin therapy	15.8%	12.8%	59.5%	<0.001

CRP: C-Reactive Protein; PDA: Patent Ductus Arteriosus;

Figure legends

Figure 1: Flow-chart