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**Original Research Article**

# Validation of weight, insulin like growth factor 1, neonatal retinopathy of prematurity for detecting retinopathy of prematurity among Indian preterm neonates

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## ABSTRACT

**Background:** Among the premature infants, WINROP (weight, insulin like growth factor 1, neonatal retinopathy of prematurity), a web- based retinopathy of prematurity (ROP) risk algorithm, uses postnatal weight gain in predicting the risk of severe ROP. This retrospective study assess the sensitivity and specificity of WINROP algorithm to predict proliferative ROP (type 1, type 2).
**Methods:** This was a tertiary hospital based retrospective study conducted in level 3 - NICU from February - November 2018. The data was entered in WINROP website. 45 neonates enrolled in the study, were classified as either alarm given (increased risk of severe ROP) or not given (no risk of severe ROP/ no ROP). Timing of alarm was also noted.
**Result:** 10 neonates (22%) had severe ROP requiring treatment. The mean gestational age was 30 weeks and mean birth weight was 1275 grams. In this study, sensitivity to WINROP online system was found to be 90%, specificity of 48.6%, positive predictive value of 33.3% and negative predictive value of 94.4%. The median time from alarm to treatment was 6 weeks (3-8 weeks).
**Conclusion:** WINROP algorithm has a good sensitivity in detection of treatable ROP.

**Keywords:** Algorithm, Insulin like growth factor 1, Preterm, ROP, Weight gain, WINROP

## INTRODUCTION

Retinopathy of prematurity (ROP) is one of the common causes of preventable blindness in neonates & it is a disorder of developing retina of preterm neonates[1]. The common risk factors for developing ROP are prematurity, oxygen therapy, hypoxia/hyperoxia, neonatal sepsis, blood transfusion, persistence of ductus arteriosus and recurrent apnea.[1,2]

At present, National Neonatology Forum of India advocates screening of all neonates <34 week of gestation or a birth weight of <1750 grams and in neonates >1750 with presence of risk factors. Current govt of India also advocates similar gestational cut off and weight <2000 grams.[3]

In a country like India still considerable challenge with trained ophthalmologist for screening of ROP, especially in peripheral and rural areas.[4] Some of the western countries have developed risk factors based approach to screen neonates at high risk of ROP. One of this approach is an algorithm called WINROP, which is based on post-natal weight gain as a predictive model for occurrence of treatable ROP.[5] This algorithm has been widely tested and validated in developed countries. There is lack of data from developing countries like India, where there is a need to detect neonates at risk of developing treatable ROP. Hence the need of the study.

## METHODS

This was a hospital based retrospective study conducted in level 3- NICU from February - November 2018. The individual patient data were collected from hospital records and entered in predesigned proforma. Data that were collected included general demographic data, gestational age, birth weight, serial postnatal weights and neonatal morbidities, complications and known risk factors for ROP. Gestational age was calculated based on the 1st trimester scan/ LMP.

ROP in our study was classified according to International Classification of ROP.[6] For the purpose of data entry into the WINROP algorithm the following neonates were included in the study: a) gestational age <32 week, b) neonates having serial weight measurements. Neonates with life-threatening major malformations or weight gain >450 grams per week were excluded from the study.[7]

The data was entered in the WINROP website. All neonates were classified as either alarm given(increased risk of severe ROP) or not given (no risk of severe ROP/ no ROP). Timing of alarm was also noted. The data was entered till the alarm signaled or a post menstrual age of 36 weeks. Based on the ROP outcome found on ophthalmological examination the sensitivity & specificity of WINROP algorithm predicting Type 1 ROP was calculated

### *Statistical analysis*

The data was analyzed by standard methods using SPSS 22 version software. Patient demographic and outcome data were analyzed using percentages and mean / median for continuous variables. Chi square test was used for categorical variables. Sensitivity/specificity/PPV/NPV and accuracy of WINROP was also calculated. A p-value of <0.05 was considered statistically significant.

## RESULTS

A total of 116 neonates were screened during the study period, out of which 59 were more than 32 weeks and 3 had major congenital malformations and hence were excluded from the study. Of the remaining 9 neonates(<32 weeks) did not have patient data and hence were excluded from the study. Therefore, a total of 45 neonates were enrolled in the study.

Among these 10 neonates (22%) had severe ROP requiring treatment (Table 1). There were no major differences among the groups with respect to gender. The mean gestational age was 30 weeks and mean birth weight was 1275 grams (Table 1).

**Table 1: The demographic data and risk factors.**

| | Alarm | No alarm | All infants |
|---|---|---|---|
| High grade ROP | 9 | 1 | 10(22%) |
| Low grade/ no ROP | 18 | 17 | 35 |
| Total | 27 | 18 | 45 |
| Gestational age(weeks) | 29(26-32) | 30.4(27-32) | 30.1(26-32) |
| Birth weight(grams) | 1060(600-1400) | 1336(850-2040) | 1275(600-2040) |

Table 2 Shows the risk factors among the neonates who developed severe ROP. Among these factors low gestational age, low birth weight, ventilation, CPAP, oxygen therapy, PRBC transfusion, IVH, PDA and BPD were significantly associated with development of severe ROP.

**Table 2: Risk factors.**

| Risk factors | Type 1 ROP | P value |
|---|---|---|
| Gestational age(weeks) | 10(22%) | 0.011 |
| Birth weight(grams) | 10(22%) | 0.012 |
| Maternal hypertension | 4 (40%) | 0.280 |
| GDM | 0 | 0.263 |
| Antenatal steroids | 4 (40%) | 0.872 |
| Birth asphyxia | 4(40%) | 0.612 |
| RDS | 9(90%) | 0.680 |
| Surfactant | 6(60%) | 0.420 |
| Ventilation(days) | 10(23%) | 0.005 |
| CPAP(days) | 10(23%) | 0.001 |
| Duration of O2(days) | 10(23%) | 0.024 |
| PRBC transfusion | 9(41%) | 0.015 |
| Culture positive | 3(30%) | 0.153 |
| Fungal sepsis | 1(10%) | 0.338 |
| Meningitis | 1(10%) | 0.725 |
| IVH | 6(60%) | 0.003 |
| PDA-Hs | 9(90%) | 0.002 |
| BPD | 5(50%) | 0.001 |
| Phototherapy | 9(90%) | 0.370 |

The WINROP alarm occurred in 27 neonates (60%) (Table 3). The median time from birth to alarm was 1 week. In the alarm group, treatable ROP developed in 10

infants, with median time from birth to alarm was 1 week (1-4 weeks). The median time from alarm to treatment was 6 weeks (3-8 weeks). Of the 10 infants with severe ROP, 1 was not detected by WINROP as high risk.

**Table 3: WINROP algorithm association with severe ROP.**

| Alarm given | Severe ROP | | Total |
|---|---|---|---|
| | Yes | No | |
| Yes | 9 | 18 | 27 |
| No | 1 | 17 | 18 |
| Total | 10 | 35 | 45 |

**Table 4: Sensitivity and specificity of WINROP algorithm.**

| Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|
| 90% | 48.6% | 33.3% | 94.4% | 57.8% |

The gestational age for this 1 infant was 32 week, and birth weight was 1400 g which received laser treatment at 40 week of post menstrual age.

## DISCUSSION

The WINROP (weight, insulin-like growth factor 1, neonatal, retinopathy of prematurity algorithm) screening algorithm has received much attention in recent years[8,9].Itwas initially based on research that demonstrated links between postnatal measurements of weight and serum insulin-like growth factor 1 (IGF-1) levels with ROP.[8]

The model was later simplified to use postnatal weekly weight gain alone as a proxy measure of serum IGF-1levels.[9] In this web based model, the expected weight gain and actual weight gain are compared, and the differences are calculated and accumulated.[9] When the accumulated sum exceeds a critical limit, an alarm is signaled to indicate that the infant is at risk for developing severe ROP[9].The exact threshold for alarms is not revealed to the users.

**Table 5: Sensitivities and specificities of WINROP validation studies.**

| Authors | Country | No of neonates | Sensitivity | Specificity |
|---|---|---|---|---|
| Developed countries | | | | |
| Hellstrom et al[9] | Sweden | 353 | 100% | 84.5% |
| Wu et al,[10] | USA | 318 | 100% | 81.7% |
| Wu et al[11] | USA/Canada | 1706 | 98.6% | 36.2% |
| Lundgren et al[12] | Sweden | 407 | 95.7% | 23.9% |
| Piyasena et al,[13] | UK | 410 | 87.5% | 63.4% |
| Eriksson et al,[14] | Sweden | 104 | 100% | 58.6% |
| Piermarocchi et al | Italy | 377 | 83.6% | 55.2% |
| Jung et al,[15] | USA | 483 | 81.8% | 53.3% |
| Developing countries | | | | |
| Hard,[16] | Brazil | 366 | 90.5% | 55% |
| Zepeda,[17] | Mexico | 352 | 84.7% | 26.6% |
| Sun et al,[18] | China | 590 | 89.3% | 89% |
| Choi et al,[19] | South Korea | 314 | 90% | 52.6% |
| Ko et al,[20] | Taiwan | 148 | 64.7% | 55% |
| Kocak et al,[21] | Turkey | 223 | 84.3 % | 52.8% |
| **Current study** | **India** | **45** | **90%** | **48.6%** |

In developed countries the sensitivity and specificity varied between 100%-83.6% and 84.5%-23.9% respectively (Table 4). Present study showed sensitivity of 90%, specificity of 48.6% which is comparable to other studies from developing countries (sensitivity and specificity ranging from 98.5%-55% and 89%-36.2% respectively). India leads in premature births in the world, but there are considerable challenges in ROP screening in India like lack of skilled manpower, availability of treatment facilities in the peripheral settings and cost of screening. Presently this study has a sensitivity of 90%, meaning if the patient does not get any alarm then the chances of having treatable ROP is very less. Since this is a small pilot study, adequately powered study is required to validate the WINROP algorithm in detection of treatable ROP.

Limitations of the study were inadequately powered study with less sample size and Babies with SGA / with growth restrictions were not excluded.

## CONCLUSION

WINROP has a good sensitivity in detection of treatable ROP. Further a large adequately powered study is required to validate the WINROP algorithm in detection of treatable ROP.

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