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TITLE PAGE

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Abbreviations: ROP (Retinopathy of prematurity), BW(Birth weight), GA(Gestational age)

What's Known on This Subject: ROP appears in more mature babies in developing countries. It is highly recommended that every country develop its own ROP screening criteria..

What This Study Adds: By following the American guidelines (GA ≤30 weeks or BW≤1500 grams) 8.4% of ROP babies who required treatment would have been missed. According to this study, screening premature patients with GA ≤ 32 weeks or BW ≤ 2000 grams in Iran yields a sensitivity of 100% for ROP.

Abstract

Objective: To develop screening criteria for retinopathy of prematurity (ROP) in Iran and to test the applicability of existing screening criteria for this population.

Methods: In a prospective cohort study, both eyes of 1,932 infants born at or less than 37 weeks of gestation, and/or weighting 3000 grams or less were included in our study. They were screened in 9 neonatal intensive care units (NICUs) in Tehran or in our ROP clinic. The patients were examined for ROP and the need for treatment (type 1 ROP or worse). The patients were followed until retinal vascularization was completed or the patients reached 50 weeks of gestational age and no prethreshold ROP was found. All the patients were screened 4 weeks after birth or at 31 weeks of postmenstrual age whichever were later. Fundus findings and the need for treatment were recorded. A receiver operating characteristic curve was used to determine the best screening criteria for ROP. Screening criteria from other countries were applied to our patient data to determine their utility.

Main outcome measure: ROP patients requiring treatment.

Results: The mean gestational age (GA) ±SD and birth weight (BW)±SD of the screened patients were 32±2.7 weeks and 1713 ±516g, respectively. Using criteria of GA≤32 weeks or BW ≤2000 yielded sensitivity and specificity of 100% and 28.1%, respectively, for treatment requiring ROP regardless of clinical comorbidities. Following screening recommendations of American Academy of Ophthalmology, we would miss 25.7% of ROP and 8.4%ROP requiring treatment in our cohort.

Conclusion: In Iran the screening criteria for finding ROP requiring treatment differ from those of other countries. Different criteria need to be applied on a regional basis.

Keywords: Iran, neonatal, pediatrics, retinopathy of prematurity, screening.

Introduction

Retinopathy of Prematurity (ROP) is the leading cause of avoidable blindness in premature infants.[1] We are now experiencing the "third epidemic" of ROP as blindness from ROP is becoming an increasing problem in the developing world.[2] The proportion of blindness due to ROP varies greatly among countries, and in addition to neonatal care, it is influenced by the availability of effective screening and treatment programs.[3] Timely screening and treatment is critical to reducing unfavorable outcomes including blindness in premature patients.[4]

Severe ROP is increasingly seen in more mature infants in developing countries, especially when considered to their counterparts in developed countries. It is recommended that each country develop and employ their own specific regional screening criteria appropriate for their local population.[4] The latest American Academy of Pediatrics (AAP) screening guidelines for ROP recommends mandatory screening for infants with birth weights (BW)≤1500 grams (g) or gestational ages (GA) ≤30 weeks.[5] These guidelines have been shown to be inadequate for screening in developing countries.[6-8]

To date no screening criteria has been published for Iran. The aim of the present study was to evaluate the applicability of current American ROP screening criteria in Iran and to develop ROP screening criteria that can provide a safe and efficient method for identifying babies who require ROP treatment

Methods:

Infants born at ≤37th week of gestation, and/or weighting 3000 g or less were initially screened at the 31st week of GA or 4 weeks after birth, whichever was later, from November 2012 to November 2013. These patients were screened at 9 NICUs in Tehran or in the Farabi Eye Hospital ROP Clinic (the largest ROP center in Iran) after being referred from outside hospitals/NICUs in Iran. The location and severity of ROP was recorded for each infant

according to the International Classification of Retinopathy of Prematurity. [9]The patients were screened by experts in ROP screening (AF, RR, MR, RK, AK).

Institutional Review Board (IRB)/Ethics Committee approval was obtained from the Farabi Eye Hospital. The study protocol adhered to the tenets of the Declaration of Helsinki. Informed consents were obtained from the parents or guardians of the babies enrolled in the study.

Nearly half of the patients were screened in neonatal intensive care units (NICUs) and the remainder were referred on an outpatient basis for evaluation. Depending on the results of the initial fundus examination, the next examinations were performed every 2 to 21 days until one of the following criteria for termination was reached:1) zone III retinal vascularization attained without previous zone I or II ROP if the patient was more than 35weeks of gestational age or 2) full retinal vascularization was observed or 3) the patient reached postmenstrual age of 50 weeks and no pre-threshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP was present.[5]

The need for treatment was based on the Early Treatment of ROP (ETROP) study and was confirmed by at least two of the experienced ophthalmologists mentioned above. The ETROP trial recommended considering treatment for an eye with any of the following criteria of type 1ROP: [10]

Zone I, any stage ROP with plus disease;

Zone I, stage 3 ROP with or without plus disease;

And zone II, stage 2 or 3 ROP with plus disease.

A receiver operating characteristic curve (ROC) was used to identify the best screening criteria to identify patients with ROP requiring treatment. The ROC curve plots true positive rate (or sensitivity) against false positive rate (or 1-specificity) at different threshold settings.. Birth weight and gestational aged cut offs were combined to form many sets of criteria for the

ROC. Sensitivity and specificity were determined for each threshold separately. The scenario with the lowest birth weight and gestational age which achieved 100% sensitivity was considered the best. To compare the applicability of different screening criteria in the world to our population, criteria used in Turkey, the United States, the United Kingdom, Latin America, and china were applied to our data.We highlighted these regions because they represent criteria used in both the developed and developing world, the latter of which mirrors the situation in Iran. The sensitivity and specificity using these criteria were assessed in our population and the frequency of missed cases of ROP when these criteria were applied to our cohort are reported.

Mean GA and BW were compared between the no-ROP versus ROP group as well as between patients with ROP who did and did not require treatment using a t- test for statistical significance.

Results:

One thousand, nine hundred thirty two infants with either a birth weight ≤ 3000gand/or gestational age (GA) of ≤37 weeks were screened. The mean age±SD of examined patients was 32±2.7 weeks (range: 24-37weeks).The mean birth weight ±SD of screened patients was 1713±516 g (range 600-3000 g).

The mean BW±SD was 1861±474g and 1372 ±441g in the no-ROP and ROP groups, respectively (mean difference: 449, 95% CI: 443 to 535, P<0.001) and GA ±SD was 33±2.2 weeks in no- ROP group and 29 ±2.5 in the ROP group (mean difference: 3.1, 95% CI:2.9 to 3.4,P<0.001).

The mean BW ±SD was 1767±498 g in patients with ROP who did not require treatment versus 1145±336 g among ROP patients who did require treatment (mean difference: 622, 95% CI: 564 to 679, P<0.001). GA ±SDwas32.5±2.6 weeks and 28.5±2.1 weeks in ROP

patients who did not and did require treatment, respectively (mean difference: 4.0, 95% CI: 3.7 to 4.3, P <0.001).

Figure 1 provides the distribution of gestational age and birth weight with the proportion of affected babies with ROP. Systemic disease factors available for review were compared between patients with and without ROP. The presence of intubation, twin birth, transfusion, acute respiratory distress syndrome, intraventricular hemorrhage, sepsis, photo-therapy, small gestational age, and/or oxygen therapy were compared between patients with and without ROP (Table 1)

ROP was diagnosed in both eyes of 570 (30.0%, 95% CI: 28.0% to 32.2%) patients. and among these 161(8.3% of all patients) required treatment in both eyes. Stage 4 or 5 ROP was seen in 1.4% of ROP patients while lower stages (1,2, or 3) were seen in 98.6% of ROP patients.

Using ROC curve the Area Under the Curve (AUC) for ROP detection was 0.815 (95% CI: 0.794 to 0.836) and 0.778 (95% CI: 0.775 to 0.801), for gestational age and birth weight, respectively. Also, the AUC for ROP requiring treatment was 0.877 (95% CI: 0.853 to 0.902) for gestational age and 0.851 (95% CI: 0.822 to 0.888) for birth weight.

By considering only one factor, a screening threshold of BW ≤2300 g or GA≤35 weeks, would result in 100% sensitively. Using only one of these factors would result in screening of more patients than the health system could bear and would not be cost-effective. In order to find an appropriate screening threshold we considered both GA and BW and defined several potential screening criteria for which sensitivity and specificity were calculated (Table 2). Among these possibilities, a threshold of GA≤32 weeks and/or BW≤2000 g yielded a sensitivity of 93.7% and specificity of 33.8% for identifying any ROP and a sensitivity of 100% and specificity of 28.1% for identifying ROP patients who required treatment. This criteria was considered the best option because it possessed a 100% sensitivity for identifying patients with ROP requiring treatment (Table 2).

The applicability of different regional screening criteria for diagnosing ROP requiring treatment was tested in this Iranian cohort (Table 3).Following screening recommendations of American Academy of Ophthalmology, 25.4% of ROP would be missed as would 8.4% of

ROP requiring treatment. Conversely, using Turkish criteria 2.9% of ROP would be missed without any cases of ROP requiring treatment being missed.

Discussion:

ROP is a significant cause of blindness that requires creative approaches to reducing ocular morbidity. In this study, ROP was diagnosed in both eyes of 570 (30%) patients and161 (out of 1932) (8.3%) patients required treatment. Findings from studies in several developing countries (those with human development index rankings in the range 31–100) are consistent with our results.[3]ROP incidences have been reported to be 34.4% in Egypt (152 patients),[11] 34% in Oman (73 patients),[12] 47% in India (165 patients),[13] and 56% in Saudi Arabia (174 patients)[14]. An earlier study from 2003-2007 in Iran identified an incidence of 34.5%.[15]

In our study 8.3% of our ROP patients required treatment which is similar to the 9.8% of Egyptian patients requiring treatment.[11] In comparison, 5% of infants examined in the United States, United Kingdom, and Canada required treatment .[16-18]

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The mean gestational age for the babies in the Egyptian study[11] was31.02 ± 2.13 weeks (152 patients), which was similar to our cohort but higher than other studies including Goble et al.'s[19] examination of 1611 infants from six centers in Birmingham, UK (29.1 weeks). We found that babies who had ROP had significantly lower birth weight and lower GA compared to those without ROP. In addition, patients with ROP who did not require treatment had greater GA and higher BW when compared to their counterparts who required treatment. We did not find any of the systemic disease factors examined to be significantly associated with ROP development.

Suggested screening guidelines in Saudi Arabia identify at risk patients as having a GA at birth of ≤ 32 weeks and a BW of ≤ 1500 g.[4] Binkhathlan et al suggested widening the screening criteria in India to include 34-week GA infants and[14]screening all babies weighing ≤ 1700 g has also been recommended.[13]In Canada[20]and the UK, screening all infants younger than 30 weeks GA or with lower than 1200 g BW and less than 32 weeks GA or less than

1501 g BW has been suggested. [18,21] ROP screening thresholds were set higher in other developing countries such as Turkey and Saudi Arabia[8,14]with studies in Saudi Arabia, India and China recommending considering screening more mature infants in their protocols to avoid missing treatable ROP.[7,14,22,23]

In Ecuador, where the threshold for screening was a birth weight of1500 g, several initially unexamined infants presented with inoperable stage 5 ROP, so the criteria were changed the following year to 1901g and/or 37 weeks of GA.[3]

There are several significant regional differences in ROP incidence and proportion of ROP related blindness. More mature infants develop ROP in developing countries. Differences in screening criteria are the result in differences in ROP incidence and innate differences in at-risk populations. The use of different screening guidelines may be partly be responsible for differences in the reported rates of ROP between countries. Additionally, genetics, ethnicity, and difference in NICU care may be responsible for differences in ROP incidences and outcomes. Socio-economic status and differences in resources may also influence care protocols and the ability to screen patients which ultimately influences outcomes and reported incidences. The proportion of ROP related blindness also varies greatly and depends on several factors including degree of national development which may influence the availability of neonatal care, general neonatal outcomes, and the existence of effective screening and treatment protocols.

We sought to develop new screening guidelines for ROP in Iran. The ideal ROP guidelines will not miss any ROP patients that require treatment while minimizing exams of patients with mild or no retinopathy which result in increased costs as well as unnecessary exams and stress for fragile neonates.[24]The importance efficient use of health care resources is particularly heightened in the developing world where resource limitations, such as physicians trained in ROP care, exist. Applying American guidelines to our patients who have resulted in 8.4 % of ROP requiring treatment being missed and although the use of Turkish guidelines would yield

100% sensitivity in our population it would result in unnecessary examinations and create an extra strain on the health care system. We found that screening of premature infants with GA ≤32 weeks and/or BW ≤2000, which falls between the Turkish and American criteria, has 100% sensitivity of identifying ROP patients who require treatment while limiting unnecessary examinations.

Accurate delineation of the population of premature infants who are at risk for this potentially blinding condition is necessary, as it provides the evidence on which to base screening guidelines. The United Kingdom, the United States, and Canada [20]along with China and other countries[25],[26], have developed evidence based screening criteria which continue to be reviewed as the population of infants who are at risk changes over time.[5,18,27]

Though preliminary results of growth-based ROP prediction modeling are promising, and models such as WINROP have the potential to reduce the number of unnecessary and stressful examinations, they are not yet adequately sensitive to be proposed for changing screening practices.[28]

There are several limitations of this study. Referral criteria used in the 9 referring NICUs were standardized. Outpatients, however, were referred by neonatologists who were not necessarily using the same criteria. In addition, infants from outside the nine NICUs may have been referred on an outpatient basis to other providers and were therefore not captured in our study. The incidence data reported here may therefore not reflect the true incidence in the entirety of Iran. Different methods of assessing GA may have been across NICUs which would have influenced GA data. We did not consider risk factors beyond GA and birth weight because of heterogeneity in reporting risk factors among different NICU centers and limitations in the availability of this information from patients who were referred to us from outside as. outpatients. Thus it would be prudent to recommend screening more mature high-risk patients at the discretion of the neonatologist.

In summary, screening guidelines used in highly developed countries are not generalizable to all environments and will miss a high number of ROP patients and risk the development blindness. ROP screening guidelines need to be tailored to local populations and continue to evolve over. We recommend screening premature patients with GA of ≤32 weeks and or BW of ≤2000 g in Iran.

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Table 1: Comparing risk factors in ROP positive and no-ROP groups

		Total	ROP		Diff	95% CI		P
			No	Yes		Lower	Upper	
Intubation	No	1249 (90.3%)	871 (90.1%)	378 (90.9%)				
	Yes	134 (9.7%)	96 (9.9%)	38 (9.1%)	0.8%	-2.6%	4.2%	0.648 *
Number of Twins	1	1261 (67.3%)	895 (68.3%)	366 (64.8%)	3.50%	-1.1%	8.2%	0.121 ‡
	2	489 (26.1%)	333 (25.4%)	156 (27.6%)	-2.20%	-6.6%	2.2%	
	3	109 (5.8%)	69 (5.3%)	40 (7.1%)	-1.80%	-4.2%	0.6%	
	4+	16 (0.9%)	13 (1.0%)	3 (0.5%)	0.50%	-0.3%	1.2%	
Transfusion	No	1035 (72.0%)	721 (71.7%)	314 (72.5%)				
	Yes	403 (28.0%)	284 (28.3%)	119 (27.5%)	0.8%	-4.3%	5.8%	0.764 *
ARDS	No	313 (22.2%)	211 (21.5%)	102 (23.9%)				
	Yes	1094 (77.8%)	770 (78.5%)	324 (76.1%)	2.4%	-2.3%	7.2%	0.313 *
IVH	No	1390 (96.1%)	976 (96.5%)	414 (95.2%)				
	Yes	56 (3.9%)	35 (3.5%)	21 (4.8%)	-1.4%	-3.5%	0.8%	0.213 *
Sepsis	No	815 (56.4%)	568 (56.2%)	247 (57.0%)				
	Yes	629 (43.6%)	443 (43.8%)	186 (43.0%)	0.9%	-4.7%	6.5%	0.762 *
Phototheray	No	319 (22.0%)	221 (21.8%)	98 (22.6%)				
	Yes	1129 (78.0%)	793 (78.2%)	336 (77.4%)	0.8%	-3.9%	5.5%	0.741 *
SGA	No	1249 (66.9%)	873 (66.6%)	376 (67.4%)				
	Yes	619 (33.1%)	437 (33.4%)	182 (32.6%)	0.7%	-3.9%	5.4%	0.648 *
Oxygen therapy (days)	Mean ± SD	14.5 ± 46.7	15.1 ± 55.1	13 ± 15.1	2.1	-3.2	7.4	0.367 ‡
	Median (IQR)	8 (3 to 18)	8 (3 to 18)	7 (2 to 18)				

Discrepancy between the numbers and total number caused by missing values in each variable

ARDS=Acute respiratory distress syndrome

IVH=intraventricular hemorrhage.

SGA=Small for gestational age.

- **Based on Chi-Square test.**

‡ Based on Mann-Whitney test.

Table- 2: Sensitivity (dark boxes) and specificity (light gray boxes) of different GA and BW thresholds in identifying patients with ROP and those with ROP requiring treatment using receiver operating characteristic curves.

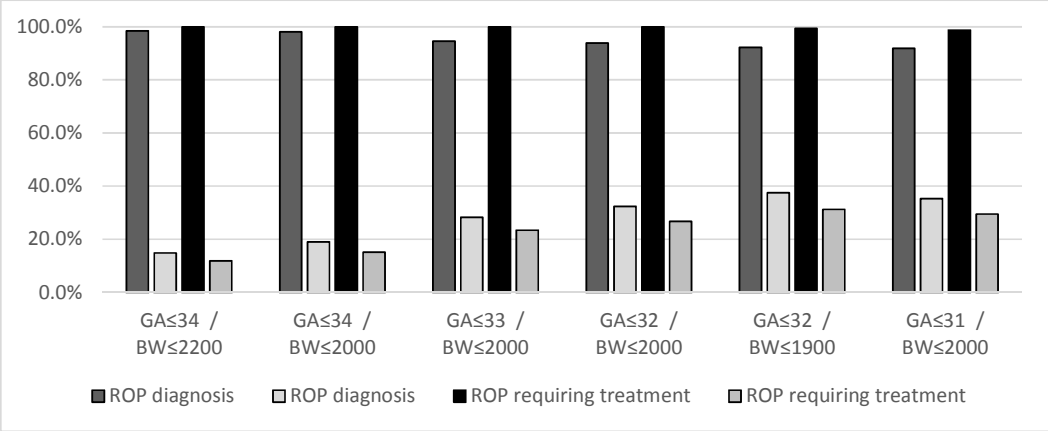

Table 3. Testing different cut-off point to find ROP patients requiring treatment using receiver operating characteristic curves.

	Criteria	Definition	TP	TN	FP	FN	Sensitivity		Sensitivity	
							%	95% CI	%	95% CI
ROP	Modified(Ours)	GA≤32 or BW≤2000	535	428	898	35	93.9%	91.5 to 95.7	32.3%	29.8 to 34.2
	US	GA<30.1 / BW <1501	425	936	390	145	74.6%	70.8 to 78.1	70.6%	68.1 to 73.0
	Turkish	GA≤34 / BW≤2000	559	252	1074	11	98.1%	96.6 to 99.0	19.0%	16.9 to 21.2
	Chinese	GA≤34 / BW≤2000	559	252	1074	11	98.1%	96.6 to 99.0	19.0%	16.9 to 21.2
	Latin America	GA≤32 / BW≤1500	501	715	611	69	87.9%	84.9 to 90.4	53.9%	51.2 to 56.6
	UK	GA<32 / BW<1501	453	865	461	117	79.5%	75.9 to 82.7	65.2%	62.6 to 67.8
ROP treatment	Modified (Ours)	GA≤32 or BW≤2000	161	463	1272	0	100.0%	98.4 to 100	26.7%	24.6 to 28.8
	US	GA<30.1 / BW <1501	147	1067	668	14	91.3%	86.6 to 95.6	61.5%	59.2 to 63.8
	Turkish	GA≤34 / BW≤2000	161	263	1472	0	100.0%	98.4 to 100	15.2%	13.5 to 16.9
	Chinese	GA≤34 / BW≤2000	161	263	1472	0	100.0%	98.4 to 100	15.2%	13.5 to 16.9
	Latin America	GA≤32 / BW≤1500	158	781	954	3	98.1%	94.7 to 99.6	45.0%	42.7 to 47.4
	UK	GA<32 / BW<1501	150	971	764	11	93.2%	88.1 to 96.6	56.0%	53.6 to 58.3

TP=True positive, TN=True negative, FP=False positive, FN=False negative, CI=Confidence interval

Figure legend:

Figure 1: Distribution of gestational age (a) and birth weight (b) with the proportion of patients with ROP.

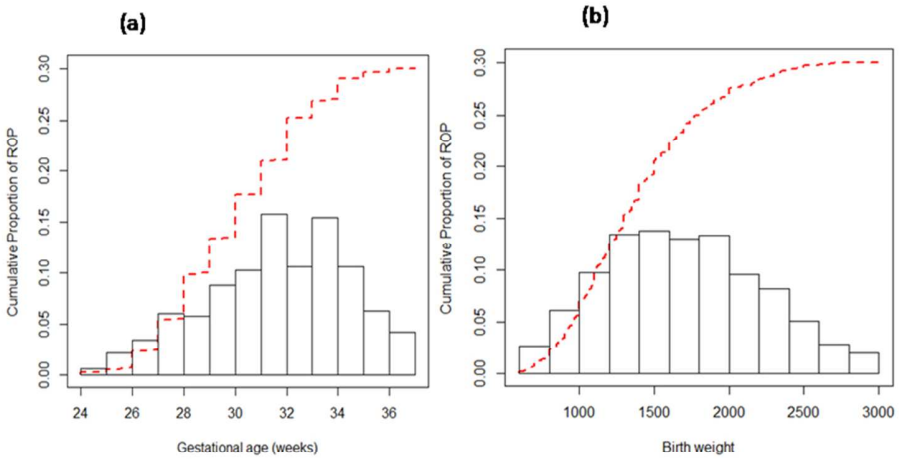

Figure 1: Distribution of gestational age (a) and birth weight (b) with the proportion of patients with ROP.
254x190mm (96 x 96 DPI)