



Frequency of retinopathy of prematurity at a tertiary referral center

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ABSTRACT

Background: With advances in medical facilities and increased survival of premature infants, the prevalence of retinopathy of prematurity (ROP) has increased. This study aimed to determine the frequency of ROP and its associated risk factors.

Methods: This descriptive-analytical, retrospective study included all premature infants with a birth weight (BW) $\leq 2,500$ g and/or gestational age (GA) ≤ 35 weeks who were referred to Imam Khomeini Hospital in Ahvaz, Iran, for ROP screening over a 7-year period from April 2013 to April 2020. Demographic criteria, associated risk factors, and findings of eye examinations were collected and analyzed.

Results: Of the 812 at-risk infants screened, 807 met the inclusion criteria. ROP was observed in 316 (39.0%) of the 807 premature infants, with types I and II in 142 (45.0%) and 174 (55.0%) infants, respectively. The mean GA (29.6 ± 2.5 weeks versus 30.7 ± 2.5 weeks) and BW ($1,203.6 \pm 382.8$ g versus $1,333.5 \pm 386.5$ g) were significantly lower in infants with ROP than in those without ROP (both $P < 0.001$). GA ($r = 0.80$; $P < 0.001$) and BW ($r = 0.85$; $P < 0.001$) had a strong positive correlation with ROP, and the correlation increased as GA and BW decreased (all $P < 0.001$). Associated risk factors in infants with ROP, in order of frequency, were oxygen therapy (22.8%), respiratory distress (16.1%), phototherapy (14.6%), blood transfusion (5.7%), apnea (4.1%), mechanical ventilation (1.6%), and intraventricular hemorrhage (0.9%). Multivariate regression analyses showed low GA and BW (both $P < 0.05$) as independent predictors of ROP.

Conclusions: The frequency of ROP in premature infants was slightly higher than the average range reported for domestic and foreign statistics. Low BW and GA were independent predictors of ROP.

KEY WORDS

low birth weight, premature infant, retinopathy of prematurity, frequency, risk factors, oxygen therapy, respiratory distress, phototherapy, blood transfusion, apnea, mechanical ventilation, intraventricular hemorrhage

INTRODUCTION

Retinopathy of prematurity (ROP), formerly known as “retrolental fibroplasia,” is a retinal disease of infants [1]. It is a preventable cause of blindness in children. In premature infants, retinal vascular completion occurs in the extrauterine environment. Numerous factors can disrupt the process of vascular development or “neovascularization,” which leads to ROP in infants [2]. Gestational age (GA) and birth weight (BW) are major risk factors for ROP, with other factors being less significantly associated with ROP [3].

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How to cite this article: Kasiri N, Kasiri A, Farrahi F, Mirdehghan MS, Kasiri R. Frequency of retinopathy of prematurity at a tertiary referral center. *Med Hypothesis Discov Innov Ophthalmol*. 2021 Winter; 10(4): 179-184. <https://doi.org/10.51329/mehdiophthal1436>

Received: 23 September 2021; Accepted: 09 November 2021



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In the last decade, the prevalence of ROP-related blindness has increased, particularly in developing countries. ROP is the main cause of blindness in China, east and southern Asia, eastern Europe, Latin America, and middle-income countries [4].

The prevalence of ROP in different parts of Iran varies from 5.6% to 70% [5-8]. ROP remains a major risk factor for blindness worldwide. Premature infants face a lifelong risk of visual disabilities and ophthalmic complications. Therefore, to reduce the overall rate of complications, lifelong ophthalmology follow-ups should be advised to parents and guardians [9].

ROP affects the retinal arteries in premature infants and can lead to visual impairments ranging from minor defects in visual acuity to retinal detachment and blindness. Risk factors for this disease include preterm delivery, particularly before gestation week 31, and a BW < 1,500 g. Apnea, maternal problems (diabetes, preeclampsia, and maternal smoking), intraventricular hemorrhage (IVH), respiratory disorders, vitamin E deficiency, heart disease, elevated blood carbon dioxide, acidosis, hypoxemia, bradycardia, oxygen uptake, increased oxygen consumption, and mechanical ventilation are other causes [10-12].

Other risk factors include respiratory distress syndrome, ethnicity, neonatal infection, and bronchopulmonary dysplasia. Predictors of ROP include underweight and a low intrauterine age [4, 13]. ROP is preventable. Further, if diagnosed early, it can be treated; otherwise, it is progressive and leads to blindness [14].

To our knowledge, the frequency and associated risk factors for ROP in premature infants have not been investigated in Ahvaz, Iran. Therefore, the present study was aimed at determining the frequency of ROP and its associated risk factors in premature infants referred to the Imam Khomeini Hospital in Ahvaz, using a 7-year retrospective sample.

METHODS

This descriptive-analytical, retrospective study was conducted on premature infants referred to Imam Khomeini Hospital in Ahvaz, Iran, during 2013-2020 for ROP screening. Medical records of all neonates referred from hospitals throughout the Khuzestan province to the Imam Khomeini Referral Hospital in Ahvaz for ROP screening were reviewed. The study received approval from the research committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS) (approval code: IR.AJUMS.HGOLESTAN.REC.1398.028).

Information on GA (based on the first day of the last menstrual period or first-trimester ultrasound and confirmation by physical examination of the infant), pregnancy weight, sex, IVH, in vitro fertilization (IVF), oxygen therapy, respiratory distress, mechanical ventilator, apnea, blood transfusions, and phototherapy were collected from hospital records and via telephone calls to parents if the records were incomplete. Infants with a BW \leq 2,500 g and/or GA \leq 35 weeks, who survived until screening, were included. We excluded infants with no documentation of final ROP outcome, loss to follow-up, or death before examination [15]. Infants with life-threatening systemic abnormalities, symptoms of Norrie disease, non-ROP-related media opacities that precluded retinal examination, congenital hydrocephalus, congenital cyanotic heart disease, and referral after 10 weeks post-birth were also excluded.

The first examination of infants with GA \leq 27 weeks was conducted at 31 weeks. Infants aged 28–32 weeks were examined at 4–6 weeks post-birth or 31–33 postmenstrual weeks, whichever was later [15]. To achieve a satisfactory pharmacological mydriasis, topical tropicamide 0.5% (Mydrax; Sina Darou, Tehran, Iran) and phenylephrine 1% (Sina Darou) eye drops were administered. All screening and follow-up examinations were performed by two vitreoretinal surgery fellows (A.K. and F.F.) using an indirect ophthalmoscope (Welch Allyn Inc., Skaneateles Falls, NY, USA) with 20- or 30-diopter lenses (VOLK Optical, Mentor, OH, USA). A sterile eyelid speculum and scleral depressor were routinely used.

The ROP classification followed the recommendations outlined by the American Academy of Pediatrics, American Academy of Ophthalmology, and American Association for Pediatric Ophthalmology and Strabismus [16]. Treatment indications were based on the Early Treatment for Retinopathy of Prematurity study [17]. We recorded demographic variables (sex, GA, and BW); use of blood transfusion, oxygen therapy, phototherapy, or mechanical ventilation; occurrence of respiratory distress, apnea, or IVH; and IVF [3].

Collected data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The data normality assumption was verified using the Kolmogorov–Smirnov test. Quantitative data are expressed as mean and standard deviation, while qualitative data are expressed as number and percentage. The independent *t*-test was used to compare ROP and no-ROP groups. Correlation between ROP and GA or BW was analyzed using Pearson's product–moment correlation statistics. Logistic regression was used to determine independent and significant factors associated with ROP. The level of statistical significance was set at $P < 0.05$ for all analyses.

RESULTS

The total number of at-risk infants screened was 812 (382 [47.0%] boys and 430 [52.9%] girls). Of these, 807 were premature infants with a BW \leq 2,500 g and/or GA \leq 35 weeks. Among premature infants, 491 (61.0%) had no ROP, while 316 (39.0%) had ROP, of whom 142 (45.0%) had type 1 ROP and 174 (55.0%) had type 2 ROP (Figure 1). The mean GA (29.6 ± 2.5 weeks versus 30.7 ± 2.5 weeks) and BW ($1,203.6 \pm 382.8$ g versus $1,333.5 \pm 386.5$ g) were significantly lower in the ROP group than in the no-ROP group (both $P < 0.001$). However, the two groups did not differ ($P = 0.243$) significantly with respect to the sex distribution (ROP group: 154 (48.7%) boys and 162 (51.3%) girls; no-ROP group: 228 (46.0%) boys and 268 (54.0%) girls). We have excluded five infants who failed to have inclusion criteria, yet, all had no-ROP.

Table 1 shows a strong positive correlation between GA and ROP ($r = 0.80$; $P < 0.001$), with a correlation coefficient that increased with reducing GA (all $P < 0.001$). In most infants with ROP (62.7%), the GA range was 29–32 weeks (Table 1). Table 2 shows a strong positive correlation between BW and ROP ($r = 0.85$; $P < 0.001$). The correlation coefficient increased with reduction in BW (all $P < 0.001$). In most infants with ROP (38.0%), the BW range was 1,201–1,500 g (Table 2).

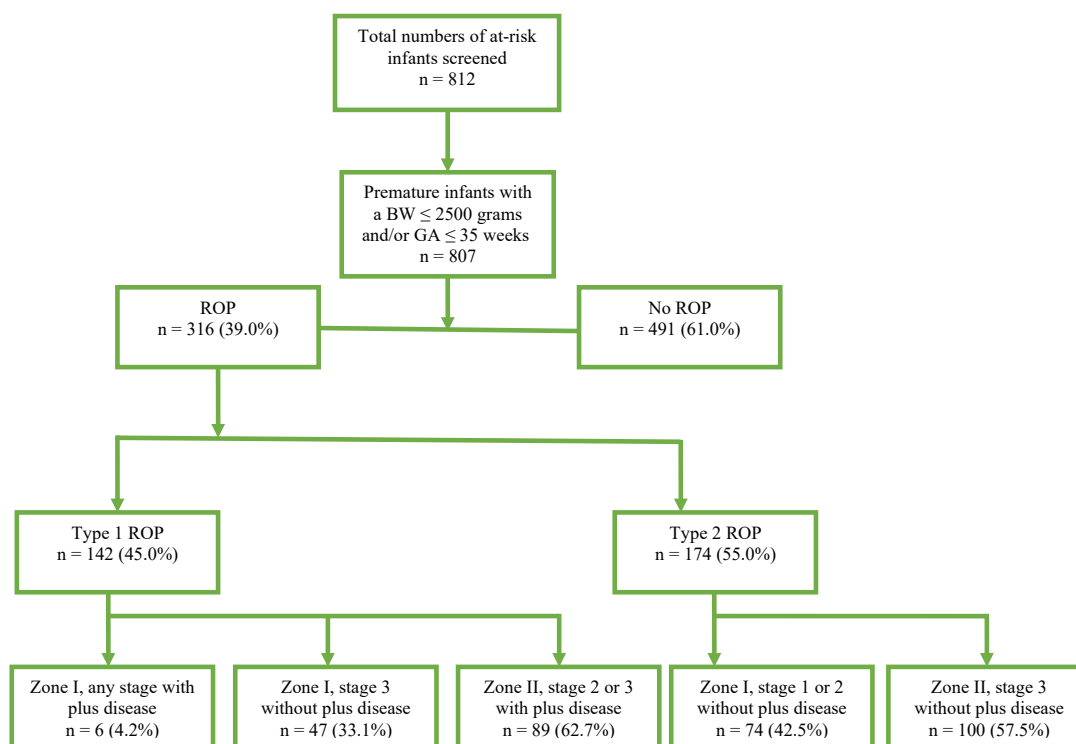


Figure 1. Flowchart of the screened infants referred to the Imam Khomeini Hospital in Ahvaz, Iran, from 2013 to 2020. Abbreviations: BW, birth weight; GA, gestational age; ROP, retinopathy of prematurity; n, number; %, percentage.

Table 1. Correlation between retinopathy of prematurity and gestational age in premature infants

Gestational age	Number of screened infants		Type of ROP		P-value*	r
	Total	ROP	Type I	Type II		
≤ 28 weeks, n (%)	206 (25.3)	87 (27.5)	56 (39.4)	31 (17.8)	< 0.001	+ 0.90
29–32 weeks, n (%)	446 (55.0)	198 (62.7)	78 (55.0)	120 (69.0)	< 0.001	+ 0.85
33–35 weeks, n (%)	160 (19.7)	31 (9.8)	8 (5.6)	23 (13.2)	< 0.001	+ 0.85
Total, n (%)	812 (100.0)	316 (100.0)	142 (100.0)	174 (100.0)	< 0.001	+ 0.80

Abbreviations: ROP, retinopathy of prematurity; w, weeks; n, number; %, percentage. *Pearson's product-moment correlation. P-values < 0.05 are shown in bold.

Table 2. Correlation between retinopathy of prematurity and birth weight in premature infants

Birth Weight	Number of screened infants		Type of ROP		P-value	r
	Total	ROP	Type I	Type II		
≤ 1,000 (g), n (%)	148 (18.2)	72 (22.8)	35 (24.6)	37 (21.3)	< 0.001	+ 0.95
1,001–1,200 (g), n (%)	208 (25.6)	94 (29.7)	44 (31.0)	50 (28.7)	< 0.001	+ 0.90
1,201–1,500 (g), n (%)	326 (40.2)	120 (38.0)	50 (35.0)	70 (40.2)	< 0.001	+ 0.90
1,501–2,000 (g), n (%)	125 (15.4)	30 (9.5)	13 (9.1)	17 (9.8)	< 0.001	+ 0.70
2,001–2,500 (g), n (%)	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001	+ 0.50
Total	812 (100.0)	316 (100.0)	142 (100.0)	174 (100.0)	< 0.001	+ 0.85

Abbreviations: ROP, retinopathy of prematurity; w, weeks; n, number; %, percentage. *Pearson's product-moment correlation. P-values < 0.05 are shown in bold.

Risk factors for ROP by frequency of occurrence were oxygen therapy (n = 72, 22.8%), respiratory distress (n = 51, 16.1%), phototherapy (n = 46, 14.6%), blood transfusion (n = 18, 5.7%), apnea (n = 13, 4.1%), mechanical ventilator (n = 5, 1.6%), and IVH (n = 3, 0.9%). The multivariate regression analyses showed low GA (28–32 weeks, $P = 0.027$; < 28 weeks, $P = 0.046$), and BW (1,200–1,500 g, $P = 0.011$; 1,000–1,200 g, $P = 0.039$) were independent predictors of ROP.

DISCUSSION

In our study, among 807 included neonates, ROP was detected in 316 premature infants, of whom 142 infants (45.0%) had type I and 174 (55.0%) had type II ROP. In infants with ROP, the mean GA was 29.6 ± 2.5 weeks, and the mean BW was $1,203.6 \pm 382.8$ g, which were significantly lower than in infants with no ROP. GA and BW had strong positive correlations with ROP, and the correlation strengthened as GA and BW reduced. Low GA and BW were independent predictors of ROP.

In a systematic review and meta-analysis, Azami et al. analyzed 42 primary studies from Iran for ROP risk factors, with an overall sample size of 18,000 premature infants [18] and found an estimated prevalence of 23.5% (95% confidence interval: 20.4–26.8). Heterogeneity was high (95.6%) because of differences in geographic regions and provinces or varying inclusion criteria in terms of GA and BW. In addition, diversity in terms of inpatient/outpatient care was an issue. Some studies examined the prevalence of ROP in neonates admitted to the neonatal intensive care unit (NICU), and others included neonates referred to outpatient ophthalmology clinics [18]. Although the rate of ROP showed an increasing trend in Iran over the past two decades, this was not statistically significant [18]. In the present study, the frequency of ROP was 39.0%, which is higher than the national rate and could be due to being Imam Khomeini Hospital as a tertiary care center in Khuzestan province.

Multiple studies have identified lower GA and BW, higher number of days of oxygen therapy, mechanical ventilation, hyperglycemia, sepsis, blood transfusion, inadequate weight gain during the first 2 weeks, and IVH as risk factors for ROP, with low GA and BW being the most consistent risk factors [18]. Likewise, GA and BW had strong positive correlations with ROP in the current study. Associated risk factors in infants with ROP in order of frequency were oxygen therapy, respiratory distress, phototherapy, blood transfusion, apnea, mechanical ventilation, and IVH. Low GA and BW were independent predictors of ROP.

Karkhaneh et al. [19] screened 185 infants with a BW ≤ 2,500 g and/or GA ≤ 37 weeks at the Farabi Hospital in Tehran, Iran. They observed ROP in 20.5% of neonates with a BW < 1,500 grams and 26.2% of neonates with a BW < 1,250 grams, while the BW was < 2,000 g in all infants with ROP. Similarly, none of our infants with ROP had BW > 2,000 grams, and 52.5% had a BW < 1,200 grams. They found a significant relationship between the incidence of ROP and blood transfusion, respiratory distress syndrome, and phototherapy. However, there was no significant relationship with oxygen consumption. In their study, ROP was observed in premature infants weighing < 1,000 g [19]. We found that low GA and BW were independent predictors of ROP. Fouladinejad et al. [20] demonstrated that the use of oxygen therapy was a risk factor for ROP; this was recorded in 22.8% of premature infants with ROP in the present study and was the most frequent among the listed risk factors.

Basiri et al. [21] screened 80 infants with GA < 34 weeks, of which 24 (30%) infants had ROP and those with ROP had BW ≤ 1,500 g. There were statistically significant relationships of ROP with GA, BW, need for resuscitation, use of inotropic drugs, 1- and 5-min Apgar scores, and duration of oxygen therapy [21]. In the present study, the frequency of ROP was higher than that in the study by Basir et al. (39.0% versus 30%). However, we also observed ROP mostly (90.5%) in infants with BW ≤ 1,500 g, and oxygen therapy was also the most frequently associated risk factor, seen in 72 (22.8%) infants of our cohort. Similar to the current study,

mean GA and BW in infants with ROP were significantly less in infants with ROP than in those without ROP [21], and low GA and BW had significant correlations with ROP [21].

Ahmadpour-kacho et al. [22] found that, of 256 hospitalized premature infants, 180 (70%) developed some degree of ROP. The mean GA and BW in infants with ROP were significantly lower in infants with ROP than in those without ROP [22], consistent with the present study. The sex distribution was similar to that in our study (50% versus 52.9% girls). However, compared to their results, the incidence of ROP in the present study was lower (39%).

Daraie et al. [23] screened 270 premature infants with a BW \leq 2,000 g and/or GA \leq 37 weeks, of which 55.2% were boys, which was higher compared to the current study (47%). Only 2.6% of infants with ROP had received high levels of oxygen therapy in their study, while in the current study, 22.8% of infants with ROP had received oxygen therapy. None of the infants with BW $>$ 1,500 g in their study developed ROP [23]; similarly, $>$ 90% of infants in our study had a BW \leq 1,500 g. The relationship of BW and oxygen therapy with the incidence of ROP was significant but that with sex and GA was not significant in their study [23]. Our study found significantly lower BW and GA in infants with ROP than in those without ROP, and no significant difference in sex distribution was detected.

In a study involving 108 premature infants with a BW $<$ 2,000 g or GA $<$ 36 weeks, Yang et al. [24] found an ROP incidence rate of 25% and concluded that low BW and GA were risk factors for the development of ROP. Infants with ROP had a significantly lower mean BW ($1,267 \pm 341$ g) and GA (29.7 ± 2.7 weeks) than those without ROP ($1,703 \pm 368$ g and 32.3 ± 2.2 weeks). Detected risk factors for ROP were artificial ventilation for over 5 days, chronic lung disease, periventricular leukomalacia, respiratory distress syndrome, IVH, congenital heart disease, and sepsis [24]. Similarly, ROP had a significantly strong correlation with low GA and BW in the current study, and the magnitude of correlation increased with decreasing GA or BW. Multivariate regression analyses showed that low GA and BW were independent predictors of ROP.

Alpay et al. [25] screened 330 infants with a BW \leq 34 weeks who were admitted to the NICU, of which 52.4% were boys, which was higher compared to the current study (47%). ROP was detected in 32.1% of infants, consistent with our results (39%). Type I ROP accounted for 5.4% of screened infants in their cohort and 17.5% of screened infants in our study. Similarly, mean GA and BW were significantly lower in infants with ROP, and oxygen therapy was the most common associated risk factor. Type 1 ROP was detected in 11.3% and 1.1% of infants with a BW \leq 1,500 and $>$ 1,500 grams, respectively [25]. This was lower compared to our study, in which type 1 ROP was detected in 19% of infants with a BW \leq 1,500 g and in 10% of infants with a BW $>$ 1,500 g.

We reported the frequency of ROP and its associated risk factors in Khuzestan, the southern province of Iran, over a 7-year period. ROP is a common cause of preventable blindness in childhood worldwide. Therefore, the results could be helpful in delaying or diminishing the burden of this disease. Regarding risk factors for ROP, Azimi et al. [18] reported use of continuous positive-pressure ventilation, septicemia, oxygen saturation $>$ 50%, and a 1-min Apgar score with an odds ratio (95% confidence interval) of 3.97 (1.21–13.01), 1.96 (1.10–3.48), 8.35 (3.14–22.18), and 1.07 (0.45–1.68), respectively. Nevertheless, preeclampsia significantly decreased ROP prevalence with an odds ratio (95% confidence interval) of 0.12 (0.02–0.65) [18]. However, our study failed to address these factors. As this study was a hospital-based study; the results may not represent the real prevalence of ROP in our region. Future studies are warranted to address these limitations. Moreover, the launch of telemedicine is a breakthrough that facilitates communication between disadvantaged areas and vitreoretinal surgery fellows and should be considered in less-privileged regions, such as the Khuzestan province. Thus, screening for ROP can be improved.

CONCLUSIONS

This study included all infants with a BW \leq 2,500 g and/or GA \leq 35 weeks, who were referred from hospitals throughout Khuzestan province to Imam Khomeini Referral Hospital in Ahvaz, Iran, for ROP screening. The frequency of ROP was 39%, which was slightly higher compared to previous studies. Most cases were type II ROP, and $>$ 90% had a BW $<$ 1,500 g. Low BW and young GA were independent predictors of ROP.

ETHICAL DECLARATIONS

Ethical approval: The study received approval from the research committee of AJUMS (approval code: IR.AJUMS.HGOLESTAN.REC.1398.028).

Conflict of interest: None.

FUNDING

None.

ACKNOWLEDGEMENTS

This paper is derived from the medical doctoral thesis of Niusha Kasiri. The authors thank the Deputy of Research and Technology Affairs and Ophthalmology Department of AJUMS. Furthermore, we acknowledge Dr. Ali Kasiri as a supervisor of this research, and declare his paternal relationship with Niusha Kasiri and Rozhin Kasiri, with all having made valid co-author contributions based on International Committee of Medical Journal Editors authorship criteria.

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