Al Ameen J Med Sci 2024;17(4):331-337 ● US National Library of Medicine enlisted journal ● ISSN 0974-1143

ORIGINAL ARTICLE CODEN: AAJMBG

A study of retinopathy of prematurity at a tertiary care centre in Western Maharashtra

Ajit K. Joshi[1], Medha M.B[1*], Pravin Hankare[1], Sara Dhanawade[2] and Shalaka Kshirsagar[1]

[1]Department of Ophthalmology, Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Wanlesswadi, Sangli-416414, Maharashtra, India and [2]Department of Pediatrics, Bharati Vidyapeeth (DU) Medical College and Hospital, Wanlesswadi, Sangli-416414, Maharashtra, India

Received: 19th March 2024; ***Accepted:*** 28th July 2024; ***Published:*** 01st October 2024

Abstract: *Background:* Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disease which can cause blindness if not diagnosed early. The various risk factors associated with ROP other than pre mature birth and low birth weight are high flow oxygen, sepsis , multiple transfusions, multiple births, respiratory distress syndrome, apnoeic episodes, intraventricular haemorrhage. Poor antenatal care, unavailability, poor access and poorly monitored neonatal care are some of the factors contributing to increase in the number of ROP cases in developing countries. *Objective:* To study ROP in preterm and high risk neonates in a tertiary care hospital. To assess and record changes of ROP and the associated risk factors in the study population.. To document the staging of ROP. To determine the outcome of Retinopathy of Prematurity and the different modalities of treatment used. *Material & Method:* This study was conducted on 262 eyes of 131 neonates over a period of 18 months. All Pre term neonates having gestational age of less than or equal to 32 weeks and birth weight less than or equal to 1500gms and other older neonates more than 32 weeks of gestation and more than 1500gms of birth weight with risk factors for developing Retinopathy of prematurity (i.e on oxygen supplementation, Respiratory distress syndrome, Sepsis, Multiple blood transfusions, Apnoeic episodes, Intraventricular haemorrhage) , admitted and referred to our institute within the study period were screened for Retinopathy of Prematurity. Neonates observed having ROP were followed up till complete regression of ROP. *Results:* In our study ROP was observed in 18.32 % of neonates. There was significant relation of birth weight and gestational age with retinopathy of prematurity. Also risk factors like Respiratory distress syndrome and mechanical ventilation were significantly associated with retinopathy of prematurity. The treatment requiring cases of Retinopathy of Prematurity were 6.11% i.e 8 neonates. All the treatable cases were given ROP Laser therapy while 6 neonates were also given intra- vitreal injections of bevacizumab. *Conclusion:* Low birth weight, Prematurity, Respiratory distress syndrome, Mechanical ventilation were the risk factors significantly associated with ROP. Prompt screening and early diagnosis of ROP can help in reducing devastating complications and thus prevent blindness.

Keywords: Retinopathy of Prematurity, Prematurity, Respiratory distress syndrome, Low birth weight, Mechanical ventilation, Bevacizumab.

Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disease which can cause blindness if not diagnosed early [1]. In premature infants retinal vessels are not completely developed and continue to develop even after birth. If this development becomes aberrant, it leads to Retinopathy of prematurity. ROP is recognised by the World Health Organization in its VISION 2020: Right to Sightprogram as an important, avoidable cause of blindness in children [2]. In India, incidence of ROP ranges 20-52% among pre term & low birth weight neonates [3].

The incidence of ROP is dependent on the availability, access to and quality of neonatal care. The various risk factors associated with ROP other than pre mature birth and low birth weight are high flow oxygen, sepsis , multiple transfusions, multiple births, respiratory distress syndrome, apnoeic episodes, intraventricular haemorrhage [4]. Poor

antenatal care, unavailability, poor access and poorly monitored neonatal care are some of the factors contributing to increase in the number of ROP cases in developing countries.

The purpose of this study is to increase awareness about Retinopathy of prematurity by prompt screening and diagnosing Retinopathy of prematurity cases, identifying the stage and type of the disease, among Pre mature infants less than or equal to 32 weeks of GA and birth weight less than or equal to 1500gms, also those infants having risk factors for development of Retinopathy of prematurity, thereby prevent the end stage sequel of the disease.

Material and Methods

This study was conducted, after approval from the institutional ethics committee, among the neonates from the neonatal intensive care unit (NICU) of our institute for a duration of 18 months. All Pre term neonates having gestational age of less than or equal to 32 weeks and birth weight less than 1500gms and other older neonates more than 32 weeks of gestation and more than 1500gms of birth weight with risk factors for developing Retinopathy of prematurity (i.e on oxygen supplementation, Respiratory distress syndrome, Sepsis, Multiple blood transfusions, Apnoeic episodes, Intraventricular hemorrhage), admitted and referred to our institute within the study period.

Patients whose guardian/parent were not willing to give consent to participate in the study and neonates having media opacity in the eye were not included in the study. As per the protocol all neonates who were above 28 weeks were screened in the 4th week of life. Informed written consent of the guardian of subject to participate in the study was taken. Tropicamide 0.8% with phenylepherine 2.5% eye drops is used for dilating the pupils. Examination of the fund us was carried out using a binocular indirect ophthalmoscope and +20D lens under aseptic precautions after instilling topical anaesthetic 0.5% Proparacaine eye drops and applying pediatric eye speculum- Alfonso speculum along with a scleral depressor.

The demographic data and findings including stage of Retinopathy of prematurity, zone involved and type of Retinopathy of prematurity was noted and the statistical data was analysed. Laser ablation (Double frequency Nd YAG green laser 532nm) and Injection Bevacizumab (0.01ml of 0.625mg) were considered for treatment of ROP in those infants requiring treatment. All the neonates were followed up till complete vascularisation of the retina or regression of the disease. Outcome in treated neonates was noted.

Statistical Analysis:

Sample size: All study subjects presenting and referred to ophthalmology department in Bharati Vidyapeeth (DU) Medical College and Hospital, Sangli within 1 year.

Minimum sample size: Calculated by using statistical formula = 81 neonates

Minimum sample size = $\frac{Z2\ P\ (1-P)}{d2}$

with prevalence = P = 14.15% [16]
& type I error = α = 1% ; Z = 2.58
& absolute precision = d = 10%
.: Accordingly 131 neonates with 262 eyes were included which were collected within the duration of 1 year were considered for the analysis.

IBM SPSS Version 21 software was used to calculate statistics. Microsoft Excelbook 2019 was used to prepare tables and graphs. Annova test was used to compare mean between the groups. Chi-Square test was used to correlate parameters. P value < 0.05 was set for significance.

Results

In the present study, out of 262 eyes of 131neonates screened, ROP was observed in 47 eyes of 24 neonates. ROP was observed in 18.32% of the neonates screened during the study period.

Gender distribution: Out of 16 mild ROP cases 56.25% were male neonates and 43.75% were female neonates, out of 8 severe ROP neonates 50% were male neonates and 50% were female. Totally 13 male neonates were found to have ROP, 11 female neonates were found to have ROP. No relation was observed between the gender of neonates and ROP stages.

*Severe ROP / Treatment requiring ROP - Defined as zone 1 plus with any stage, zone 1 stage 3 with no plus and zone 2 stage 2 or 3 plus. All eyes with type 1 pre-threshold ROP are currently recommended for immediate treatment. Mild ROP / Observation - Defined as zone 1 stage 1 or 2 without plus disease and zone 2 stage 3 without plus disease and follow-up is recommended for such eyes P value - 0.68 (> 0.05) value not significant.

Relationship of Severity of ROP with Gestational age and Birth weight: In the present study out of 131 cases, mild ROP was observed in 16 cases, severe ROP in 8 cases and 107 cases did not have ROP. 31.81weeks was the mean gestational age observed among mild ROP cases, while 29.63 weeks was the mean gestational age observed in severe ROP cases. The study showed significant relation between severity of ROP and gestational age (P value < 0.0001). Cases with Gestational age less than 30weeks have higher chances of developing Severe ROP.

Mean birth weight of 1.36 Kg was observed in Mild ROP cases, mean birth weight of 1.16Kg was observed in Severe ROP cases. Significant relation was observed between the birth weight and severity of ROP (P value < 0.0001). Neonates having birth weight less than 1.75Kg are at greater risk to develop ROP.

Table-1: Severity of ROP and Gestational age and birth weight

	Mild ROP (n = 16)	Severe ROP (n = 8)	No ROP (n = 107)	P value
Gestational age	31.81±2.37	29.63±0.74	33.94±2.24	< 0.0001***
Birth weight	1.36±0.35	1.16±0.15	1.76±0.54	< 0.0001***

The table-1 shows the mean gestational age and mean birth weight among the neonates having mild & severe ROP as well as those without ROP. P value - <0.0001 for mean birth weight and gestational age is significant.

Risk factors for ROP: In the present study Respiratory distress syndrome was the most common risk factor observed among neonates having ROP. Among the mild ROP cases 56.25% cases had Respiratory distress syndrome out of whom 37.5% cases were on Nasal Prong and 12.50% neonates required mechanical ventilatory support. 6.25% neonates had risk factors like Twin pregnancy, Hypoglycaemic seizure, NEC and Chronic Heart disease.

Respiratory syndrome distress was present among all the 8 neonates having severe ROP, out of which, 50% cases were on Nasal prong and 50% required mechanical ventilation while 25% cases were observed with pneumonia. Respiratory distress syndrome (p<0.0001***) and Mechanical ventilation (0.0004*) were significantly associated with ROP stages.

P value for Respiratory Distress Syndrome – 0.02

P value for Mechanical ventilation – 0.0004

Both values are less than 0.05, hence significant

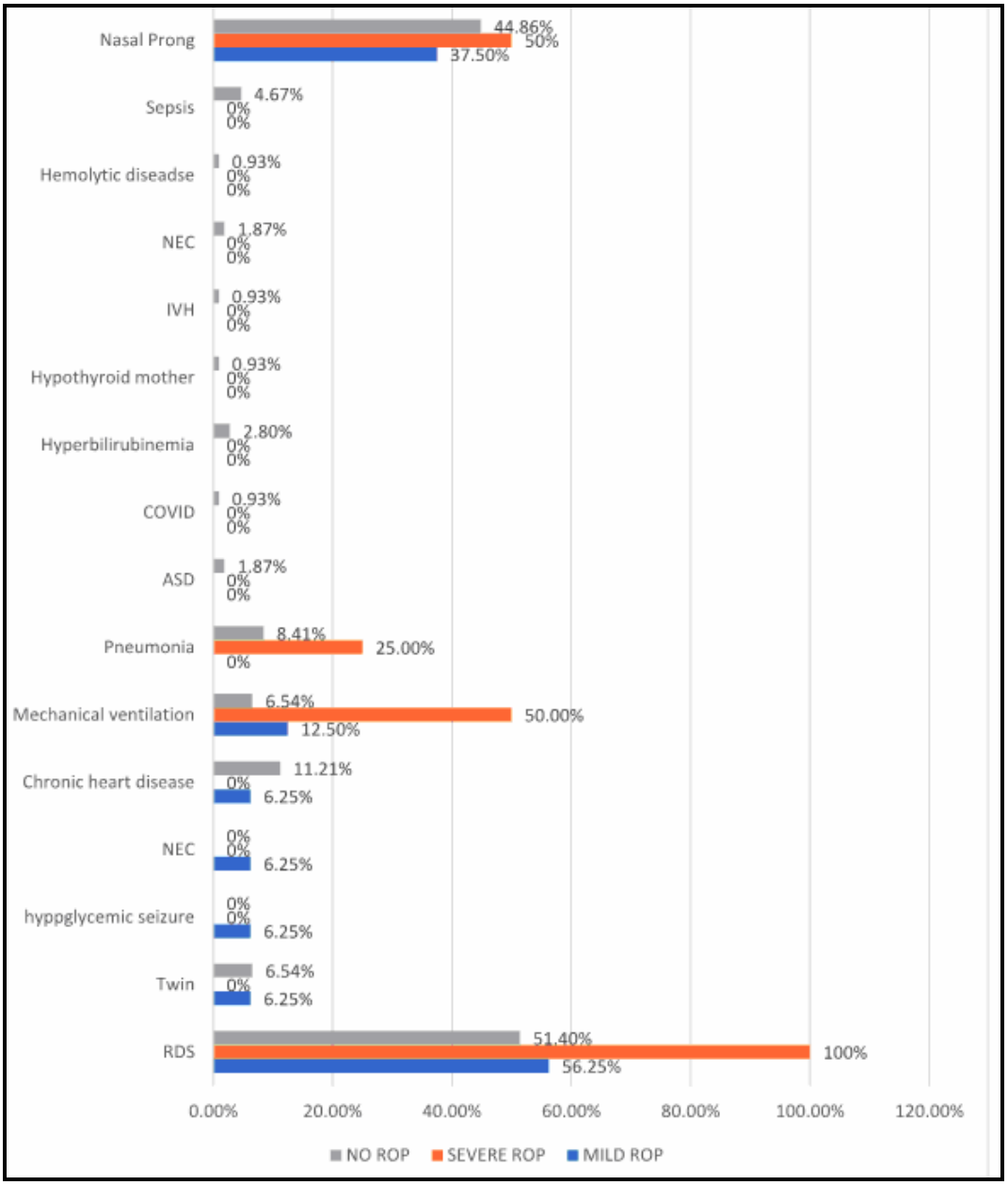
Table-2: Stage wise distribution

Stages	Mild ROP (n=16)	Severe ROP (n=8)
Stage 1	10 (62.5%)	0
Stage 2	5 (31.25%)	4 (50%)
Stage 3	1 (6.25%)	1 (12.5%)
AP – ROP	0	2 (25%)
Pre plus	0	3 (37.5%)
Plus	0	3 (37.5%)

The above table-2 tells us about the distribution of ROP according to the stage.

Stage-wise Distribution: In the present study among Mild ROP cases - 62.5% cases were seen with Stage 1, 31.25% cases of Stage 2 and 6.25% cases were observed with Stage 3, where as among Severe ROP cases, 50% cases were observed with Stage 2, 12.5% cases of Stage 3, 25% cases of AP ROP, and 37.5% each cases of Pre Plus and Plus staging.

Fig-1: Risk Factors



The above Figure-1 shows the various risk factors associated with ROP.

Zone-wise Distribution: In the present study among mild ROP cases, 62.5% cases had Zone 3 involvement and 37.5% cases involved Zone 2. In Severe ROP cases 25% cases had involvement of zone 1 and 75% cases with zone 2.

The table-3 tells us about the distribution of ROP according to the Zone.

Table-3: Zone-wise Distribution

Stages	Mild ROP (n=16)	Severe ROP (n=8)	No ROP (n=101)
No involvement (Mature Retina)	0	0	32 (29.91%)
Zone 1	0	2 (25%)	1 (0.93%)
Zone 2	6 (37.5%)	6 (75%)	17 (16.83%)
Zone 3	10 (62.5%)	0	57 (53.27%)

Table-4: Treatment-wise distribution		
Treatment required	**No of cases**	**Percentage (%)**
YES	8	6.11
NO	123	93.89

The above table-4 is representing the percentage of neonates receiving treatment. In the present study 16 eyes of 8 neonates i.e 6.11% neonates required treatment.

Treatment: Neonates who required treatment were treated with Laser ablation using 532nm Double frequency Nd YAG green laser under sedation / General anaesthesia under the supervision of a neonatologist and Intra vitrealInj Bevacizumab (0.01ml of 0.625mg) undertopical anaesthesia. 25% neonates were treated with laser treatment and 75% cases were treated with intra vitrealInj Bevacizumab + Laser ablation

Table-5: Treatment		
Treatment	**No of cases**	**Percentage (%)**
Laser ablation(532nm Double frequency Nd YAG green laser)	2	25
Ing Bevacizumab + Laser ablation	6	75
Total	8	100

The above table-5 is representing the various forms of treatment for the neonates

Discussion

This was an observational, prospective study conducted among 262 eyes of 131 neonates who fulfilled the above mentioned inclusion criteria were screened for Retinopathy of Pre maturity. All the neonates were screened in the 4thweek of birth, using indirect ophthalmoscope. Vascularisation status of the retina was noted and follow up was done accordingly. Out of 262 eyes of 131 neonates, ROP was observed in 47 eyes of 24 neonates. ROP was observed in 18.32% of the neonates screened during the study period.

Among 131 neonates, 81 were male , 50 were females . Out of 17 mild ROP cases 52.94% were male neonates and 47.06% were female neonates, out of 7 severe ROP neonates 57.14% were male neonates and 42.86% were female neonates. Among 107 cases without ROP, 63.55% were male neonates and 36.45% were female neonates. There was no statistical significance seen with respect to gender in neonates developing ROP. Similarly in studies conducted by Andre Moraes Freitas et al [5], Francis Mutangana et al [6] & Yin K N et al [7] there was no statistical significance found with respect to gender in neonates developing ROP.

In 262 eyes of 131 neonates, Mild ROP was observed in 31eyes of 16 neonates i.e 11.83%, Severe ROP in 16 eyes of 8 neonates i.e 6.10% and 215 eyes of 107 neonates i.e 82.06% were without ROP. Mild ROP being considered as zone 1 stage 1 or 2 without plus disease and zone 2 stage 3 without plus disease i.e those cases which were considered for follow up & Severe ROP defined as zone 1 plus with any stage, zone 1 stage 3 with no plus and zone 2 stage 2 or 3 plus i.e those cases which were considered for treatment [8].

Similarly in a study done by Ahmet Yagmur Bas et al [9], 6.7 % of cases had severe ROP. As per study by Gillian G W Adams et al [10], treatment requiring ROP was 4%. Andr Moraes Freitas et al [5] in their study also found that treatment requiring ROP was 5%. Fortes Filho et al [11] in their study found treatment requiring ROP to be 5.8% and Xu et al [12] in their study found that treatment requiring ROP to be 6.8%. Thus the percentage of treatment requiring ROP in our study and of those mentioned above were similar.

In our study, mild ROP cases had a mean gestational age of 31.71 weeks while a mean gestational age of 29.57 weeks was observed in severe ROP cases. Our study shows a significant relation between severity of ROP and gestational age. Cases with Gestational age less than 30 weeks, have higher chances of developing Severe ROP. According to a study by AndrMoraes Freitas et al [5], mean GA in babies developing any stage of ROP was 30.7 weeks. According to a study by Ahmet Yagmur Bas et al [9], mean GA among the subjects was 28.9 weeks.

Thus a gestational age of 30 weeks and below is a significant risk factor for developing ROP according to the above mentioned studies and the same has been observed in our study as well. AP ROP in our study was found to be 8.5% of all ROP case, all of which were successfully treated. Similarly in a study conducted Gillian G W Adams et al [10]AP – ROP was seen in 8.26%. There is a similarity in the percentage of AP-ROP cases observed in our study and that of Gillian G W Adams et al[10]. 1.36kg Mean birth weight was observed in Mild ROP cases, 1.16Kg mean Birth weight was observed in Severe ROP cases. Significant relation was observed between the birth weight and severity of ROP. Neonates having birth weight less than 1.75KG are at a greater risk to develop ROP.

Tekchandani et al [13] in their study found the mean birth weight for neonates with ROP was 1.2 KG. In severe ROP babies 1.26 was the mean birth weight while in non severe ROP babies 1.29KG was the mean birth weight. Again the mean birth weight of neonates developing ROP is found to be similar in our study and that of Tekchandani et al [13]. In the present study Respiratory distress syndrome was the most common risk factor observed in ROP cases. In mild ROP cases , 56.25% cases were observed with Respiratory distress syndrome followed by 37.5% cases with oxygen supplementation by Nasal Prong, 12.50% cases neonates required mechanical ventilatory support and 6.25% each were Twin, had Hypoglycemic seizure, NEC & Chronic Heart disease. All 8 cases with severe ROP developed Respiratory syndrome distress, 50% of the severe ROP cases had oxygen supplementation by Nasal prong and 50% required mechanical ventilatory support and 25% cases were observed with pneumonia. Respiratory distress syndrome ($p<0.0001$***) and Mechanical ventilation (0.0004*) were significantly associated with ROP.

Cassie A. Ludwig et al [4]in their study stated similarly that babies with RDS had higher odds of developing ROP. AndreMoraes Freitas et al [5] in their study stated that Pulmonary diseases and IVH were the most commonly associated risk factors in babies developing ROP. Respiratory distress syndrome thus seemed to be significantly associated with developing ROP in neonates both in our study and that of Cassie A. Ludwig et al [4]. 47 eyes of 262 eyes were diagnosed to have ROP. Thus the incidence of ROP turned out to be 18.32% in our study. Similarly, Cassie A. Ludwig et al [4] in their study mentioned an incidence of ROP as 17.9% . Andre Moraes Freitas et al [5] in their study showed 33.9 % incidence of ROP. Xu et al [12] in their study stated the incidence of ROP to be 17.8%. Chaudhari et al [14] in their study stated the incidence of ROP to be 22.3%. The incidence of ROP in India is reported to vary between 38 – 51.9 % according to NNF guidelines.

In our study, treatable ROP was seen in 16 eyes of 8 neonates, out of these 2 neonates were given Laser ablation (Double frequency Nd YAG green laser 532nm), while 6 neonates were given both Laser ablation and Inj Anti – VEGF (Inj Bevacizumab 0.01ml of 0.25mg). All the 8 treatable ROP neonates were successfully treated with the outcome at the end of follow being lasered regressed ROP in both eyes. In a study conducted by Subhadra jalai et al [15], 43.9% ROP neonates were treated with Laser diode ablation, 5.6 % with surgery, 1.3 % with cryopexy, 3.1% with Laser ablation & Surgery.

Conclusion

In our study ROP was found to be significantly associated with Low birth weight, Prematurity and with risk factors like Respiratory distress syndrome, Oxygen supplementation in the form of Mechanical ventilation. Laser ablation can be considered as the standard treatment for treatable ROP, while Intra vitreal Inj. Bevacizumab is also considered for treatment, specially in AP-ROP.

Thereby we can conclude that, prompt screening and early diagnosis of ROP can help in reducing devastating complications and thus prevent blindness. However, larger and longer studies may be needed to generate appropriate guidelines.

Financial Support and sponsorship: Nil **Conflicts of interest:** There are no conflicts of interest.

References

1. Bhende PS. Retinopathy of prematurity. *Indian Journal of Ophthalmology.* 2020; 68(Suppl 1):S10.
2. Austeng D. Retinopathy of Prematurity in Infants Born before 27 Weeks of Gestation: A National Population-based Study in Sweden During 2004-2007. *Doctoral dissertation, Acta Universitatis Upsaliensis.*
3. Shukla R, Murthy GV, Gilbert C, Vidyadhar B, Mukpalkar S. Operational guidelines for ROP in India: a summary. *Indian Journal of Ophthalmology.* 2020; 68(Suppl 1):S108.
4. Ludwig CA, Chen TA, Hernandez-Boussard T, Moshfeghi AA, Moshfeghi DM. The epidemiology of retinopathy of prematurity in the United States. *Ophthalmic surgery, lasers & imaging retina.* 2017; 48(7):553.
5. Freitas AM, Mörschbächer R, Thorell MR, Rhoden EL. Incidence and risk factors for retinopathy of prematurity: a retrospective cohort study. *Int J Retina Vitreous.* 2018; 31(4):20.
6. Mutangana F, Muhizi C, Mudereva G, Noë P, Musiime S, Ngambe T et al. Retinopathy of prematurity in Rwanda: a prospective multi-centre study following introduction of screening and treatment services. *Eye.* 2020; 34(5):847-856.
7. Ng Y,Shaw D, Fielder A, Levene M. Epidemiology of retinopathy of prematurity. *The Lancet.* 1988; 332(8622):1235-1238.
8. Agarwal K, Jalali S. Classification of retinopathy of prematurity: from then till now. *Community Eye Health.* 2018; 31(101):S4.
9. Bas AY, Demirel N, Koc E, UlubasIsik D, Hirfanoglu İM, Tunc T; TR-ROP Study Group. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. *Br J Ophthalmol.* 2018; 102(12):1711-1716.
10. Adams GG, Bunce C, Xing W, Butler L, Long V, Reddy A, Dahlmann-Noor AH. Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. *BMJ Open.* 2017; 7(3):e013366.
11. Fortes Filho J, Eckert G, Procianoy L et al. Incidence and risk factors for retinopathy of prematurity in very low and in extremely low birth weight infants in a unit-based approach in southern Brazil. *Eye*. 2009; 23:25-30.
12. Yu Xu, Xiaohong Zhou, Qi Zhang, Xunda Ji, Qin Zhang, Jianxing Zhu et al; Screening for Retinopathy of Prematurity in China: A Neonatal Units-Based Prospective Study. *Invest. Ophthalmol. Vis. Sci.* 2013; 54(13):8229-8236.
13. Tekchandani U, Katoch D, Dogra MR. Five-year demographic profile of retinopathy of prematurity at a tertiary care institute in North India. *Indian J Ophthalmol.* 2021; 69:2127-2131.
14. Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care center-incidence, risk factors and outcome. *Indian Pediatr.* 2009; 46(3):219-224.
15. Molinari A, Weaver D, Jalali S. Classifying retinopathy of prematurity. *Community Eye Health.* 2017; 30(99):55-56.
16. Suryawanshi M, Bokade CM, Patil S et al. Retinopathy of prematurity: Prevalence, demographic characteristics, and outcomes at a tertiary care center in central India. *Curr Pediatr Res*. 2022; 26 (6):1448-1453.

Cite this article as: Joshi AK, Medha MB, Hankare P, Dhanawade S and Kshirsagar S. A study of retinopathy of prematurity at a tertiary care centre in Western Maharashtra. *Al Ameen J Med Sci* 2024; 17(4): 331-337.

*All correspondences to: Dr. Medha M.B, Senior Resident, Department of Ophthalmology, Bharati Vidyapeeth (DU) Medical College and Hospital, Wanlesswadi, Sangli-416414, Maharashtra, India. Email: medha.manur@gmail.com